Towards the interoperability of spontaneous reporting systems in pharmacovigilance: A maturity model approach with a sociotechnical system focus

by

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Declaration

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Date: March 2020

Abstract

It is universally accepted that all medicines have the potential to cause adverse drug reactions (ADRs) during the course of their normal therapeutic use. Drug safety surveillance during the post-marketing authorisation phase generates the majority of drug safety data, even more so than the clinical trials during the drug development process. Pharmacovigilance (PV), is based on the medical assessment of ADRs or drug-related problems, collected within organised health programmes.

PV systems, by nature, are complex. The large number, fragmentation, and complexity of existing PV systems, the equally large number of stakeholders within such systems (i.e. pharmaceutical companies, government regulatory authorities, national and international clinical regulatory bodies, healthcare workers, etc.), as well as the significant number of dimensions along which the effectiveness and efficiency could be influenced and also measured, adds to this complexity.

The primary goal of any PV system is to improve and protect patient safety by enabling health care professionals to make more informed therapeutic decisions. Achieving this goal is dependent on the successful communication of relevant ADR information from the patient to the relevant PV authority. One such method of communication is the spontaneous reporting of ADRs, which is widely regarded as the cornerstone of data generation in PV during post-marketing authorisation safety surveillance.

Currently, spontaneous reporting systems (SRSs) are faced with problems such as under-reporting and the communication of incomplete, unrepresentative, and uncontrolled data. The lack of standardisation and interoperability among these systems results in a reduced capability to detect and characterise new adverse drug interactions and ADRs.

The primary obstacle to achieving interoperability between SRSs is the fundamental difference in the purpose of the existing SRSs. Stakeholders in the PV system operate SRSs with different goals and perspectives such as maintaining regulatory compliance, mitigating financial risk, and for the protection and promotion of patient safety in public health programmes.

The aim of this study is to contribute towards the interoperability of SRSs in the PV landscape through the development of a novel maturity model with a sociotechnical system focus. The aim of the model is to promote and improve interoperability by addressing the degree of integration of systems involved, provide guidance on which system components need to be improved, as well as provide a means for measuring interoperability progress across the community of SRSs in the global PV landscape.

A multidisciplinary literature review covering PV, capability maturity models, interoperability, and sociotechnical systems served as a theoretical foundation for the development of the model. The development of the model followed an adaptation of the 8-phase procedural model for developing maturity models, proposed by Becker *et al.* (2009).

A comparison of 18 existing maturity models in the fields of: (i) PV; (ii) eHealth; (iii) eHealth/interoperability; (iv) interoperability; and (v) IT infrastructure, was conducted. The model is made up of three domains, seven subdomains, and thirty dimensions which were identified as a result of the preceding literature review and comparison of existing models.

Through a combination of verification and validation processes involving subject matter experts, the maturity model was refined. The resulting maturity model was implemented in a case study within a national regulatory authority context, to determine the generalisability and empirical validity of the model. The model was deemed a useful, unique, and valuable contribution to organisations operating SRSs, having achieved the stated aim.

Opsomming

Oor die algemeen word dit aanvaar dat alle medisyne die potensiaal het om negatiewe geneesmiddelreaksies te veroorsaak tydens hul normale terapeutiese gebruik. Dwelmveiligheidswaarneming tydens die na-bemarkingsmagtigingsfase genereer die meerderheid van dwelmveiligheidsdata, selfs meer as die kliniese proewe tydens die dwelmontwikkelingsproses. *Pharmacovigilance* (*PV*), is gebaseer op die mediese evaluering van geneesmiddelreaksies of dwelmverwante probleme, wat binne georganiseerde gesondheidsprogramme ingesamel word.

PV-stelsels is inherent kompleks. Die groot aantal, fragmentasie en kompleksiteit van bestaande *PV*-stelsels, die ewe groot aantal belanghebbendes binne hierdie stelsels (d.w.s. farmaseutiese maatskappye, staatsregulerende owerhede, nasionale en internasionale kliniese reguleringsliggame, gesondheidswerkers, ens.), sowel as die beduidende aantal dimensies waarlangs die effektiwiteit en doeltreffendheid beïnvloed kan word en ook gemeet word, dra by tot hierdie kompleksiteit.

Die primêre doel van enige *PV*-stelsel is om pasiëntveiligheid te verbeter en te beskerm deur gesondheidsorgwerkers in staat te stel om meer ingeligte terapeutiese besluite te neem. Die bereiking van hierdie doelwit is afhanklik van die suksesvolle kommunikasie van relevante geneesmiddelreaksie-inligting van die pasiënt na die betrokke *PV*-owerheid. Een sodanige kommunikasiemetode is die spontane rapportering van geneesmiddelreaksies, wat algemeen beskou word as die hoeksteen van data-opwekking in *PV* tydens die veiligheidswaarneming na bemarking.

Tans word spontane rapporteringstelsels (SRSe) gekonfronteer met probleme soos onder-rapportering en die kommunikasie van onvolledige, nie-verteenwoordigende en onbeheerde data. Die gebrek aan standardisering en interoperabiliteit tussen hierdie stelsels lei tot 'n verminderde vermoë om nuwe geneesmiddelsinteraksies en geneesmiddelreaksies na te spoor en te karakteriseer.

Die primêre struikelblok vir die bereiking van interoperabiliteit tussen SRSe is die fundamentele verskil in die doel van die bestaande SRSe. Belanghebbendes in die *PV*-stelsel bedryf SRSe met verskillende doelwitte en perspektiewe, insluitende: die handhawing van regulatoriese vereistes; die vermindering van finansiële risiko;

en die beskerming en bevordering van pasiëntveiligheid in openbare gesondheidsorgprogramme.

Die doel van hierdie studie is om by te dra tot die interoperabiliteit van SRSe in die *PV*-landskap deur die ontwikkeling van 'n nuwe en oorspronklike volwassenheidsmodel met 'n sosiotegniese stelselfokus. Die doel van die model is om interoperabiliteit te bevorder en te verbeter deur die mate van integrasie van betrokke stelsels aan te spreek, leiding te gee oor watter stelselkomponente verbeter moet word, asook om die interoperabiliteitsprogressies in die wêreldwye gemeenskap van SRSe te meet.

'n Multidissiplinêre literatuuroorsig oor *PV*, volwassenheidsmodelle, interoperabiliteit en sosiotegniese-stelsels het gedien as 'n teoretiese grondslag vir die ontwikkeling van die model. Die ontwikkeling van die model het gevolg op 'n aanpassing van die 8-fase prosedure model vir die ontwikkeling van volwassenheidsmodelle, voorgestel deur Becker *et al.* (2009).

'n Vergelyking van 18 bestaande volwassenheidsmodelle in die velde van: (i) *PV*; (ii) *eHealth*; (iii) *eHealth*/interoperabiliteit; (iv) interoperabiliteit; en (v) IT-infrastruktuur, is uitgevoer. Die model bestaan uit drie domeine, sewe subdomeine en dertig dimensies wat geïdentifiseer is as gevolg van die voorafgaande literatuuroorsig en vergelyking van bestaande modelle.

Die volwassenheidsmodel is deur 'n kombinasie van verifiërings- en valideringsprosesse, waar vakkundiges betrokke was, verfyn. Om die veralgemeenbaarheid en empiriese geldigheid van die model te bepaal, is die gevolglike volwassenheidsmodel in 'n gevallestudie, binne die nasionale konteks van 'n regulerende owerheid, geïmplementeer. Die gestelde doel van die model is bereik en die model word geag as 'n nuttige, unieke en waardevolle bydrae tot organisasies wat SRS'e bedryf.

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Contents

CONTENTS

CONTENTS

List of Figures

LIST OF FIGURES

List of Tables

Nomenclature

Acronyms

ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
AEFI	Adverse Event Following Immunization
ATC	Anatomical Therapeutic Chemical
CAP	Centrally Authorised Product
CDISC	Clinical Data Interchange Standards Consortium
CEM	Cohort Event Monitoring
CMM	Capability Maturity Model
DR	Design Requirement
DTC	Drug and Therapeutics Committee
EC	European Commission
EEA	European Economic Area
EHR	Electronic Health Record
EMA	European Medicines Agency
FDA	Food and Drug Administration
GP	General Practitioner
GS1	Global Standards One
HCP	Health Care Professional

Nomenclature

HIS	Health Information System
HIT	Health Information Technology
HL7	Health Level 7
ICH	International Conference on Harmonization
ICSR	Individual Case Safety Report
ICT	Information and Communication Technology
IDMP	International Drug Monitoring Programme
IHTSDO	International Health Terminology Standards Development Organisation
ISO	International Organisation for Standards
ISoP	International Society of Pharmacovigilance
LMIC	Low- and Middle-Income Countries
MAH	Marketing Authorisation Holder
MCC	Medicines Control Council
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MM	Maturity Model
NAP	Nationally Authorised Product
NCA	National Competent Authority
PASS	Post Authorisation Safety Study
PHP	Public Health Program
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
QPPV	Qualified Person for Pharmacovigilance

RA	Regulatory Authority
SAHPRA	South African Health Products Regulatory Authority
SDO	Standards Development Organisation
SME	Subject Matter Expert
SR	Spontaneous Reporting
SRS	Spontaneous Reporting System
STSE	Sociotechnical Systems Engineering
STS	Sociotechnical System
TSR	Targeted Spontaneous Reporting
UMC	*the* Uppsala Monitoring Centre
WHO-ART	World Health Organisation Adverse Reactions Terminology
WHO	World Health Organisation

Chapter 1

Introduction

In this chapter, the context within which the research problem exists, as well as the aims and objectives of the research are summarised. The research approach, methodology, and scope demarcation are specified. The structure of the dissertation is laid out, and a list of research outputs produced from this dissertation is provided.

1.1 Background

It is universally accepted that all medicines have the potential to cause adverse drug reactions (ADRs) during the course of their normal therapeutic use (Belton *et al.*, 1997). The terms ADR and 'side effect' are often confused for one another, or used interchangeably. A side effect is defined as being any unintended, usually predictable, effect of a pharmaceutical product, which may or may not result in harm, occurring at a normal therapeutic dosage. An ADR is different in that it is a noxious[1] and unintended response to a pharmaceutical product (World Health Organization, 2006).

Figure 1.1 relates the terms medication error, ADR, and adverse drug event (ADE). Medication errors are those which occur during prescribing, transcribing, dispensing, administering, adherence, or monitoring a pharmaceutical product. Medication errors may or may not result in the patient being harmed. An ADE can be any negative or harmful occurrence that takes place during the course of treatment, which may or may not be associated with a pharmaceutical product (World Health Organization, 2006). Figure 1.1 shows that all ADRs are a type of ADE but not vice versa. Figure 1.2 is a cause-and-effect diagram showing the various factors which may contribute to an ADE.

The World Health Organization (WHO) (2006) defines pharmacovigilance (PV) as "the science and activities relating to the detection, assessment, understanding and prevention of

[1] "Harmful, poisonous, or very unpleasant".

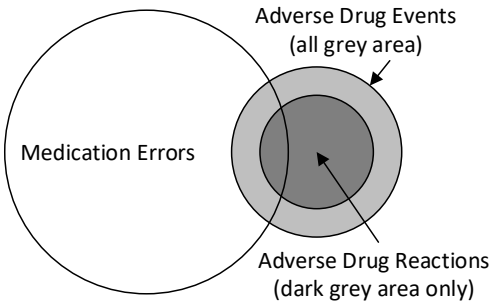

Figure 1.1: The relationship between medication errors, adverse drug events, and adverse drug reactions (Nebeker *et al.*, 2004).

adverse effects or any other possible drug-related problems". PV, often referred to more simply as patient safety, is based on the medical assessment of ADEs or drug-related problems, collected within organised health programmes. Within these programmes it is vital to be able to consistently identify the nature of events, their severity, their likelihood of occurrence and to assess causality with the suspected drug(s) or medicine(s). The primary goal of any PV system is to improve and protect the safety of the patient by enabling health care professionals (HCPs) to make more informed therapeutic decisions. The successful operation of a PV system is dependent on the successful communication of relevant ADR information from the patient experiencing the ADR to the relevant PV authority, so that the necessary action can be taken to prevent medicine related problems and reduce morbidity and mortality associated with ADRs.

ADR information can be communicated via multiple reporting methods, throughout the entire pharmaceutical drug development life cycle. The majority of ADR information is generated during the post-marketing authorisation phase of the drug life cycle (Figure 3.1). This is when a pharmaceutical company has performed all of the necessary clinical trials and safety studies for a product which they are developing with the intention of marketing within the jurisdiction of a regulatory authority (RA). Once marketing authorisation has been granted and a product enters the market, the number of patients consuming that product increases exponentially, and with that comes an increase in unexpected ADRs. Information pertaining to these ADRs is captured and communicated via a spontaneous reporting system (SRS), this is a system where the ADR information can be reported in an unsolicited, or voluntary manner, either by a health care professional (HCP), or in some instances the patients themselves.

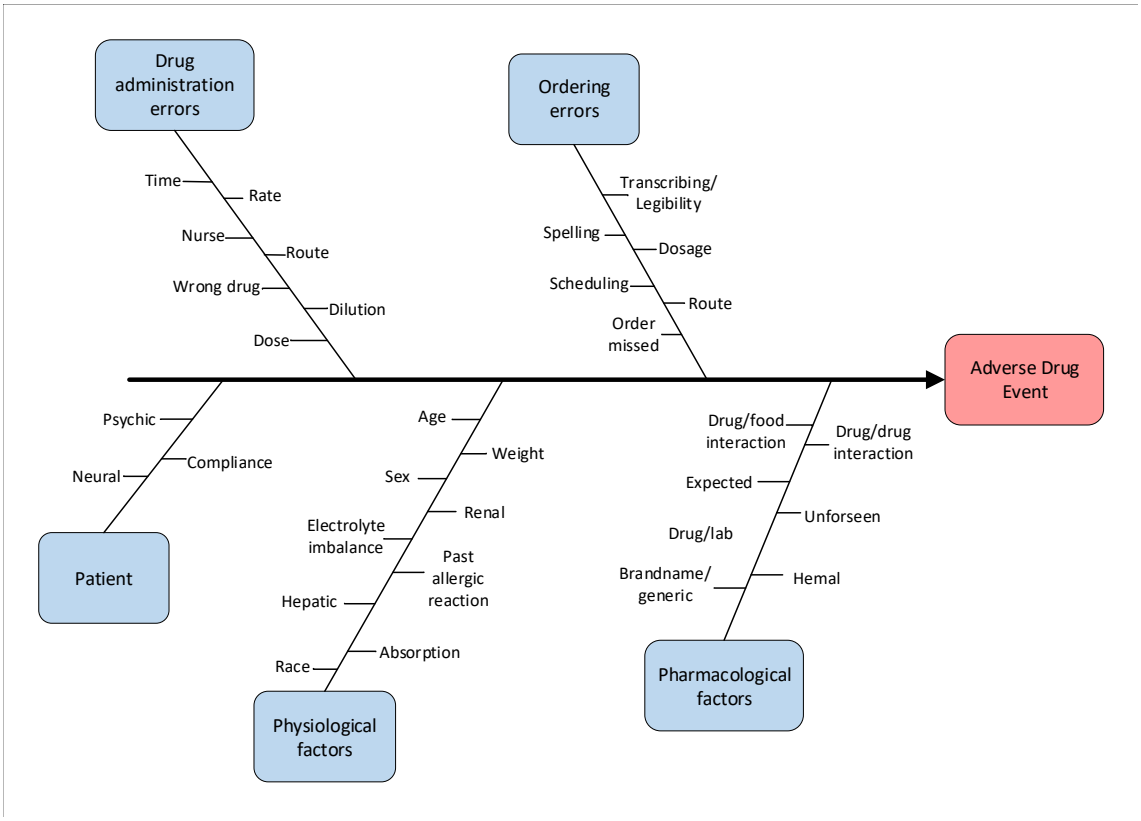

Figure 1.2: A cause-and-effect diagram showing the factors which may contribute towards an ADE.

1.1.1 The global PV landscape

The international PV landscape is difficult to characterise due to the large number and variety of stakeholders, and the number of fragmented PV systems in various countries. A simplified view of the current landscape of global PV activities can be seen in Figure 1.3. The World Health Organisation (WHO) established *the* Uppsala Monitoring Centre (*the* UMC)[1] in 1978 to co-ordinate the programme for international drug monitoring. *The* UMC, under leadership of the WHO, communicates information between its member countries and the pharmaceutical industry, regarding the benefits and risks of medicines that are used in their public healthcare programmes.

The UMC manages and maintains a SRS which is comprised of several data management tools and methods, these tools and methods are discussed in detail in Section 4.4. *The* UMC is the custodian of an Individual Case Safety Reports[2] (ICSRs) database called VigiBase. The ICSRs in VigiBase are submitted by national PV centres or RAs via reporting gateway applications such as *the* UMC's VigiFlow. Some RAs have developed their own reporting gateway applications, for example, the two largest RAs in the world, namely the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA), shown in Figure 1.3, make use of the FDA Adverse Events Reporting System (FAERS)(Li *et al.*, 2015) and EudraVigilance (Pacurariu *et al.*, 2015), respectively. These ICSRs are analysed with the objective of drawing quantitative conclusions from the input data. *The* UMC is faced with negotiating and persuading policy makers and regulators, particularly those in resource-limited and middle- to low-income countries to give pharmacovigilance the necessary attention and resources to strengthen the global system.

Supporting organisations such as the International Society of Pharmacovigilance (ISoP), as well as academia, and standards development organisations (SDOs), participate in the development of PV practices as well as training and education with respect to PV around the world. Figure 1.3 does not delineate a clear hierarchy, protocol of interaction, or division of responsibility amongst the various stakeholders, this is indicative of the lack of such high-level coordination within the global PV landscape.

[1] Stylised as '*the* UMC', by the organisation itself.

[2] An ICSR is a document which includes an identifiable patient, an identifiable reporter (HCP), as well as a drug and a suspected ADR relating to the drug. An ICSR can contain multiple drugs and suspected ADRs, but may only include one identifiable patient and only one identifiable reporter. ICSRs are discussed in detail in Chapter 4.

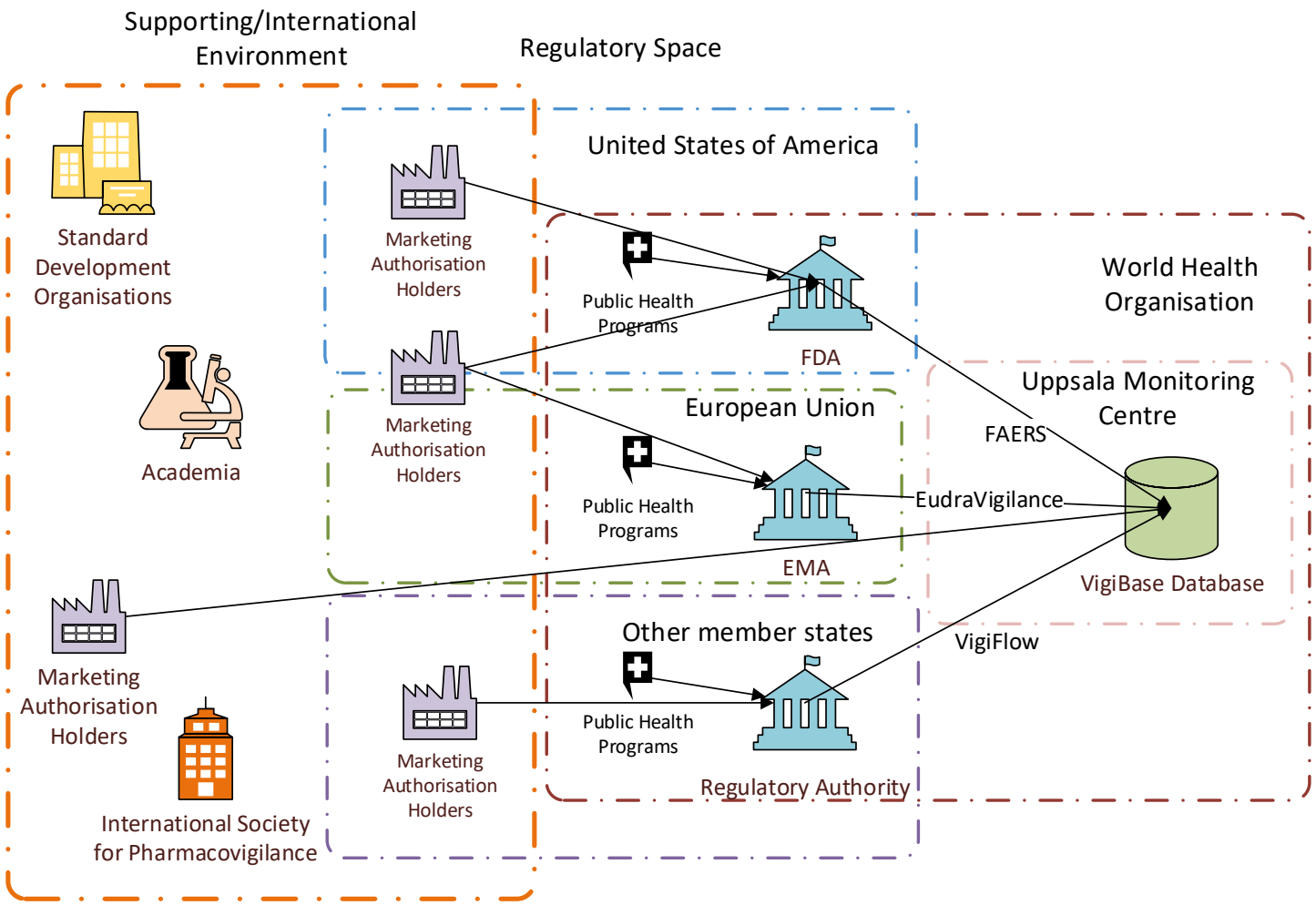

Figure 1.3: Schematic representation of the current global PV landscape.

1.1.2 Challenges in the PV landscape

The most widespread challenge facing PV is the high level of under-reporting of ADRs (Batel Marques *et al.*, 2016; Graham *et al.*, 2012; Hazell & Shakir, 2006; Koutkias & Jaulent, 2015; Lester *et al.*, 2013), typically attributed to a lack of knowledge, time and incentive (DalPan, 2014; Hasford *et al.*, 2002), which eludes to the lack of standardised reporting protocols and methodologies. Multiple sources have been identified which point to the need for a standardised SRS (Barnett, 2015; Field, 2017; Graham *et al.*, 2012; Richesson *et al.*, 2008; Shiffman *et al.*, 2003; Wong *et al.*, 2015). Problems such as under-reporting and the communication of incomplete, unrepresentative, and uncontrolled data prove to be significant barriers to detecting and characterising new adverse drug interactions and ADRs (Banerjee *et al.*, 2013).

A survey conducted by Stergiopoulos *et al.* (2016) found that hospitals with the necessary infrastructure for ADR reporting were only reporting 12% of ADRs to the respective PV centres. ADRs due to incorrect treatment plans resulted in the fourth to sixth leading cause of death in hospitalised US patients in 1994 according to a study by Lazarou *et al.* (1998). The total cost of drug related morbidity and mortality for the year 2000 in the USA was estimated at $177 billion (Ernst & Grizzle, 2001). According to the National Health Service of the United Kingdom, ADRs resulted in approximately 250 000 hospital admissions yearly, costing the health system £466 million yearly (World Health Organization, 2008).

The Strengthening Pharmaceutical Systems (SPS) Program (2011) report offers an interesting view of the socio-technical aspect of PV systems, the report highlights the reluctance of HCPs, particularly in low- and middle-income countries (LMIC) to report ADRs as they feel that in doing so, it reflects poorly on their ability to provide care of an adequate standard. Socio-economic barriers include the lack of financial incentive for HCPs to report ADRs to national PV centres (Bhagavathula *et al.*, 2016).

1.2 Problem statement

PV systems, by nature, are complex. The large number, fragmentation, and complexity of existing PV systems, the equally large number of stakeholders within such systems (i.e. pharmaceutical companies, government regulatory bodies, national and international clinical regulatory bodies, healthcare workers, etc.), as well as the significant number of dimensions along which the effectiveness and efficiency could be influenced and also measured, adds to this complexity.

Spontaneous reporting of ADRs is the cornerstone of data generation in the post-marketing authorisation phase of PV activities. Furthermore, the lack of a standardised reporting protocol across the various PV systems hinders efforts to coherently manage PV on a global scale. The primary obstacle to standardising and achieving interoperability between SRSs globally is the fundamental difference in purpose of the existing SRSs. The three main role players at the global level of pharmacovigilance are *the* UMC[1], the various MAHs, and the RAs representing governments around the world, a characterisation of the interaction between these three role players is shown in Figure 1.3. Each of these three role players has its own goals and perspectives when conducting PV:

1. *The* UMC: To successfully integrate PV data from all WHO member countries and to perform statistical analysis and continuous monitoring of the global PV landscape.

2. MAHs: To achieve and maintain regulatory compliance, mitigation of financial and market risks, as well as being able to make informed marketing decisions.

3. RAs: To protect and promote patient safety within their public health programs and thus alleviate pressure on their health system.

With this fundamental difference in the purpose of the existing SRSs in mind, it is important to note that the strength of the global PV system lies in the integration of various national and private sector PV systems. While *the* UMC offers substantial support to the WHO member countries, many of the developing member countries lack the capacity and capability to take full advantage of the services offered by *the* UMC.

1.3 Research gap

It is evident from the lack of available literature on pharmacovigilance from an engineering and systems perspective, that there is considerable potential for these disciplines to contribute to the PV body of knowledge. The vast majority of published literature relating to PV comes from a clinical perspective, typically that of health care clinicians, health care scientists, epidemiologists, and statisticians. Preliminary research results, presented in this chapter, indicate the need for a solution that would contribute and improve the interoperability of spontaneous reporting systems in PV. Although various maturity models and maturity assessment frameworks exist in the fields of eHealth, Interoperability, and IT Infrastructure, as discussed in Chapter 6; a maturity model based on the concept of the capability maturity model (CMM) has not

[1] *The* UMC is the operational unit having responsibility for the direct implementation of the WHO Programme, according to an agreement between WHO and the Government of Sweden, first signed in 1978.

been comprehensively considered in the field of pharmacovigilance and the interoperability of spontaneous reporting systems.

In order to determine the research gap, and simultaneously the uniqueness of this research a customised search protocol was developed and employed across various literature databases. The search protocol differed slightly depending on the literature database but the same basic logic was applied during each search. The search involved the use of boolean and proximity operators to find literature which met the search criteria. The following four terms were combined in various search queries and executed in the Scopus database, Web of Science database, Taylor and Francis database, and Google Scholar database:

- Pharmacovigilance OR "drug safety" OR "patient safety",
- "Spontaneous reporting system",
- "Sociotechnical system", and
- "Capability maturity model".

Table 1.1: Structured search protocol results.

	Database			
Search query	Scopus	Web of Science	Taylor & Francis	Google scholar
pharmacovigilance AND ("socio technical system" OR "capability maturity model")	0	0	0	56
pharmacovigilance AND "capability maturity model"	0	0	0	28
pharmacovigilance AND "socio technical system"	0	0	0	38
pharmacovigilance AND "socio technical system" AND "capability maturity model"	0	0	0	0
(pharmacovigilance OR "drug safety") AND ("socio technical system" OR "capability maturity model")	4	0	1	105
("drug safety" OR "patient safety") AND ("socio technical system" OR "capability maturity model")	34	13	25	1170
(pharmacovigilance OR "drug safety" OR "patient safety") AND "socio technical system" AND "capability maturity model"	0	0	0	7
(pharmacovigilance OR "drug safety") AND "socio technical system"	3	0	1	75
(pharmacovigilance OR "drug safety") AND "capability maturity model"	1	0	0	40
"spontaneous reporting system" AND "capability maturity model"	0	0	0	0
"spontaneous reporting system" AND pharmacovigilance AND ("socio technical system" OR "capability maturity model")	0	0	0	1
"spontaneous reporting system" AND ("socio technical system" OR "capability maturity model")	0	0	0	1

The combined result of these searches were eight documents, seven of which were academic journal articles addressing patient safety from an ergonomics perspective, mostly regarding the design of hospitals, as well as one PhD dissertation from Imperial College, London. The PhD dissertation focuses on the development of clinical trials by improving evidence-based risk-benefit decision-making of medicines for children (Mt-Isa, 2011). After investigating the results of the structured search protocol, a conclusion was reached that no capability maturity model for spontaneous reporting systems in PV exists. To the best knowledge of the author at the time of conducting this research there is no PVR-CMM (Pharmacovigilance Reporting Capability Maturity Model) equivalent in existence.

1.4 Aim and objectives

This dissertation seeks to contribute to the global PV landscape by achieving the research aim and supporting research objectives outlined below.

1.4.1 Aim

The aim of this research is to contribute towards the interoperability of SRSs in the PV landscape through the development of a maturity model with a sociotechnical system focus. The maturity model should be useful and of value to RAs, by providing guidance on how to manage and develop their SRSs towards interoperability.

1.4.2 Objectives

It is envisaged that the objectives which will collectively contribute towards achieving the above stated aim are:

1. To conduct a literature review on the structure of the PV landscape and to define concepts and paradigms from this literature relevant to this study.
2. To evaluate the value of interoperability in the global PV reporting system through a comprehensive and system-based evaluation of the effects of the lack of such interoperability on PV/health outcomes.
3. To identify through a comparative analysis of PV systems, the main elements that such an interoperable system would need to comprise of.
4. To identify barriers to ADR reporting.

5. To conduct a literature review on maturity models with a specific focus on the scientific and design considerations of maturity models; and define concepts and paradigms from this literature that are relevant to this study.

6. To conduct a literature review on sociotechnical systems, with a specific focus on the associated theory, and to characterise the PV system as a sociotechnical system.

7. To define the design requirements for a PV reporting capability maturity model.

   7.1. To verify the design requirements by engaging subject matter experts.

8. To search for an existing model which satisfies the design requirements.

9. To develop a maturity model for PV reporting activities, rooted in sociotechnical system theory, if such a model does not exist.

   9.1. To streamline and refine the maturity model by engaging subject matter experts, with a focus on including an industry perspective, so as to verify that the maturity model is suitable for implementation in a real world setting.

10. To design and execute a case study in which the maturity model will be implemented by a key role player in the PV landscape.

    10.1. To analyse the findings and results of the case study.

11. To validate the model by determining whether the model can achieve its stated aims, as well as the extent of the models generalisability.

1.5 Scope demarcation

There exist multiple channels via which the reporting of ADRs can take place. This research focuses on the spontaneous reporting of ADRs during the post-marketing phase of the pharmaceutical product life cycle. Spontaneous reporting is considered the cornerstone of data generation in PV (Pal *et al.*, 2013). A functioning spontaneous reporting system is considered one of the minimum requirements by the WHO, for countries conducting PV activities (World Health Organization, 2010). To improve PV on a global level, the interoperability of SRSs is paramount, the demonstrable benefits of interoperability can be found in Chapter 3. This dissertation culminates with the presentation of a maturity model which can be used to assess the capability and interoperability maturity of SRSs. Improved PV outcomes rely on the statistical analysis of data. At present, the availability, accuracy, and format of the PV data is a problem widely cited in literature, and discussed in Chapter 3. This research is not

bound by application to one context; but rather considers PV across a spectrum of contexts from resource-limited to world leading PV systems such as that of the European Union. This research is not bound by application to one role player in the global PV system; but rather takes a general approach to studying PV in a global context.

1.6 Document structure

The structure of this research was designed to guide the reader from understanding the background and context of the real-world problem, to understanding the underlying theory on which the model development is based, before the model that has been developed is finally presented. A brief description of the contents of each chapter can be found below.

Chapter 1: Introduction

In this chapter, the context within which the research problem exists, as well as the aims and objectives of the research are summarised. The research methodology and document structure are also described.

Chapter 2: Research methodology

In this chapter, the research philosophy is discussed, as well as the research approach and strategy. The chapter concludes with a discussion on the relevant research tools and techniques which are employed in this dissertation.

Chapter 3: Contextualisation

This chapter focuses on understanding the global PV landscape, what is meant by a standardised spontaneous reporting system, the challenges and barriers which affect the spontaneous reporting of ADRs, and an analysis of the effects of the lack of a standardised global PV reporting system. This chapter concludes with a discussion focussing on the extent to which standardisation could alleviate these PV challenges.

Chapter 4: Reporting of adverse drug reactions

This chapter describes the flow of information through the PV system, the key role players in the system, as well as the communication channels between the key role players in the PV system. The different methods for reporting ADRs are discussed and the current best practices are described. A comparison between methods currently in use by three selected countries is made and a comparative analysis is performed, outlining their respective differences and discrepancies. The introduction of the Electronic Health Record (EHR) as a disruptive technological innovation is discussed and a new approach, involving the use of maturity models, to addressing the challenges of under-reporting is introduced.

Chapter 5: Maturity models and interoperability

In this chapter the concept of a maturity model (MM) is explored and defined within the context of this study. The history of MMs as well as their various types and purposes is explored. The concept of interoperability is also discussed, with a particular focus on the interoperability of health information technologies (HITs) in the eHealth field. The chapter concludes with a discussion on the need to take a sociotechnical approach to introducing MMs within an eHealth context.

Chapter 6: A sociotechnical system perspective

Taking into consideration the difficulty associated with implementing standardised health information technologies (HITs) into large, complex systems, the notion of sociotechnical systems was investigated. The pharmacovigilance system was described as a sociotechnical system to gain an improved understanding of how best to design and implement HITs in these complex systems. Through the conceptualisation of the PV system as a sociotechnical system, the PVR-CMM development process was more cognizant of social, cultural, and political factors, rather than focussing solely on the technological factors.

Chapter 7: Development of the Pharmacovigilance Reporting Capability Maturity Model

This chapter deals with the creation of a model based on the CMM which can be used by governments or any entity wishing to conduct PV activities to measure and assess their PV capabilities so as to guide them towards reaching ICH E2B(R3) compliance. Thus, contributing maximally to PV on a global scale, while also receiving maximum value from the services offered by *the* UMC.

Chapter 8: Verification and model refinement

This chapter focusses on the verification and validation strategy, in the development of the second generation of the PVR-CMM. The subtle, yet significant difference between verification and validation is discussed; thereafter, the verification and validation strategy of the PVR-CMM is detailed. The tools and methods involved in this strategy are described, as well as the outcomes and results yielded through the application of these tools and methods. A deviation to the verification strategy is discussed and executed, resulting in more well founded verification outcomes.

Chapter 9: Case study implementation and external validation

This chapter introduces the second generation PVR-CMM, the resulting iteration of the maturity model after the refinements, based on the SME feedback in the previous chapter, were made. The chapter includes the design and execution of a case study, wherein the PVR-CMM

V2 is implemented in a real-world setting. The outcomes of the validation process are communicated and the overall acceptance of the PVR-CMM V2 by it's intended target audience is established. By extent to which the PVR-CMM is generalisable is determined by its ability to achieve it's stated aims.

Chapter 10: Conclusion

The final chapter contains an overview of the research presented in this dissertation, as well as confirmation that the research objectives, as stated in Section 1.4.2, have been achieved. The limitations of the research are addressed, and opportunities and recommendations for further research are discussed.

1.7 Research outputs

During the execution of this research a number of research outputs were produced:

Journal Publication:

A journal article titled "An investigation into the value of a standardised global pharmacovigilance reporting system" was published in the South African Journal of Industrial Engineering November 2017 Vol 28(3) Special Edition, pp 78-88. The contents of the paper were also presented at the 28th annual conference of the Southern African Institute for Industrial Engineering (SAIIE), held from 25-27 October 2017 in Vanderbijlpark, South Africa.
Available online: http://dx.doi.org/10.7166/28-3-1841.

International Conference Proceedings:

An international conference proceeding titled "Sociotechnical considerations for Health Information Technology design and implementation in complex and adaptive health systems" was presented at the 27th annual conference of the International Association for Management of Technology (IAMOT), held from 22 - 26 April 2018 at Aston Business School in Birmingham, United Kingdom, and was published in the conference proceedings.

1.8 Chapter 1: Conclusion

In this chapter the research was introduced through a summary of the real-world problem that PV is faced with. The problem statement, research aim, objectives, and scope demarcation were specified. The research approach, methodology, and the structure of the dissertation was laid out. Finally, a list of research outputs produced from this dissertation was provided. Following Chapter 1, Chapters 3 and 4 will involve an in depth review of the appropriate literature to further understand the challenges facing PV as well as the intricacies of ADR reporting and the current best practices involved therein.

Chapter 2

Research methods

In this chapter, the research aims and objectives are linked to the research methodology. The relevant research philosophy will be discussed, as well as the suitable research approach and methodologies that were adopted to fulfil the research aims and objectives. The research strategy, as well as the research tools and techniques which were employed in this study are justified by showing their practical applicability to the study.

2.1 Research philosophy

In order for a researcher to effectively approach the subject under investigation, it is necessary to adopt the appropriate research strategy. In order to identify the appropriate research strategy, the three components of the research paradigm must be considered. The three components of the research paradigm are the ontology, epistemology and axiology.

Ontology is concerned with the way researchers perceive reality. According to the ontological assumption, there are two means of producing valid knowledge, either objectively or subjectively. If one considers an ontological continuum, the ends of the continuum would be objectivism and subjectivism respectively. In an objective reality, the world exists and can be studied as it is by applying natural science methods to understand social reality, in a value free way (Bryman & Bell, 2015). In a subjective reality, the world exists but is studied differently by different people, where access to reality is only through social constructs (Bryman & Bell, 2015).

Saunders *et al.* (2009) state that epistemology considers what constitutes acceptable knowledge in a field of study. There exist three primary epistemological positions, namely, positivism, interpretivism, and pragmatism. Positivism involves the deductive or inductive research approach within an objective ontological paradigm. Interpretivism involves an inductive research approach within a subjective ontological paradigm. In contrast to these two epistemological

positions, the pragmatic epistemological position is one which recognises the need to take a pluralistic approach to deriving knowledge.

In this study, the pragmatic philosophical position is adopted. By taking a pragmatic approach the researcher can employ a mixed methodology approach including both qualitative and quantitative methods, including different cycles of deductive and inductive research approaches. Sale *et al.* (2002) suggest that combining research methods in this way is useful in some instances, for example in healthcare, where the complexity of the phenomena involved requires data from a large number of perspectives.

2.2 Research approach

This study is primarily non-empirical in nature and employs qualitative research methods such as literature reviews and model development based on secondary data. An empirical component of the research methodology is introduced along with the case study which is conducted as part of the research. The research conducted in this dissertation is exploratory in nature; this is partially due to the fact that a significant amount of research was required to more clearly define the problem. The purpose of exploratory research is to explore the research objectives and not necessarily to offer a conclusive solution to an existing problem. It is not uncommon for a researcher, conducting exploratory research, to change the direction of the research as a result of new insights (Saunders *et al.*, 2009). In fact, flexibility and adaptability to change can be considered an advantage of exploratory research (Stebbins, 2001).

Given that this research is primarily non-empirical, appropriate research methods must be selected for the acquisition of secondary data. Literature reviews complement exploratory research as they allow for the development of an inductive argument from the 'general' to the 'specific'. Unlike deductive arguments, inductive reasoning results in the formulation of hypotheses and theories which provide support for the truth of a conclusion, but do not necessarily guarantee the conclusion (Arthur, 1994).

2.3 Research strategy

Various research strategies exist, before selecting the appropriate research strategy the researcher must consider the type of research being conducted, either exploratory, descriptive, or explanatory. In the case of this research, the strategy is devised to support the exploratory nature of this study. For this study, a mixed methods strategy was devised. The benefit of a mixed method strategy is that it allows the researcher to address an exploratory research question with both qualitative and quantitative methods. By making use of both qualitative

and quantitative methods, the researcher has the benefit of multiple world views or paradigms to make better inferences.

In terms of research methodology, a combination of literature review, theory building, model development, and model verification and validation are used in this research endeavour. The overarching research approach that is followed is based on the 'seven step model' from Onwuegbuzie *et al.*'s (2012) "Qualitative analysis techniques for the review of the literature". The research approach is depicted in Figure 2.1 and is divided into three phases, namely: (i) exploration; (ii) interpretation and development; and (iii) communication.

The exploration phase includes Chapters 1 and 3, which make use of literature reviews to provide the necessary background to understanding the research problem, represented by steps 1 and 2 in Figure 2.1. Steps 3, 4, and 5 in Figure 2.1 results in a multidisciplinary literature review which produces outcomes from various domains, namely Chapters 4, 5 and 6; covering PV, capability maturity models; interoperability, and sociotechnical systems respectively.

Chapter 4 investigates the current workings of the global PV system, including the various role players and current best practices for the communication of ICSRs. The identified best practices, together with a thorough understanding of the reporting of ADRs, lead to the investigation of capability maturity models and interoperability in Chapter 5, and sociotechnical systems in Chapter 6.

In the interpretation phase (steps 6 and 7 in Figure 2.1), Chapters 3, 4, 5 and 6 serve as a theoretical foundation for the development of the model in Chapter 7. The outcome of this multidisciplinary literature review allows for the problem statement to be more focussed, in Section 7.3. The development of the model follows an adaptation of the 8 phase procedural model for developing maturity models, proposed by Becker *et al.* (2009).

The two step verification strategy, as described in Chapter 8, involves the selection and engagement of subject matter experts based on a selection criteria. The subject matter experts validate the model's face and construct validity via the completion of various questionnaires. By incorporating SME perspectives, the methodological rigour is strengthened due to the triangulation of the literature review findings, with inductive reasoning of the author, as well as industry perspectives gathered from a number of SMEs with diverse skill-sets and roles within the pharmaceutical industry. Further detail on the specific verification methodology that is applied, is provided in Section 8.3. Iterative refinements of the model are made, as illustrated by the cyclical relationship between steps 6 and 7 in Figure 2.1.

Upon completion of the verification activities, the final iteration of the PVR-CMM, namely the PVR-CMM V2, is deemed ready for implementation in a real world setting. Steps 8 and 9 in Figure 2.1, exist within the communication phase, this is because the PVR-CMM

2. RESEARCH METHODS

V2 is implemented within an organisation that is external to the development, verification, and refinement processes, of the interpretation and development phase. Step 8 involves the execution of a case study to determine the extent of the PVR-CMM V2's empirical validity. Empirical validity is indicated by ability of the model to achieve the stated aims, from the perspective of the end-user, as well as the extent to which a maturity model is generalisable to an environment which is external to the environment of the model during its development.

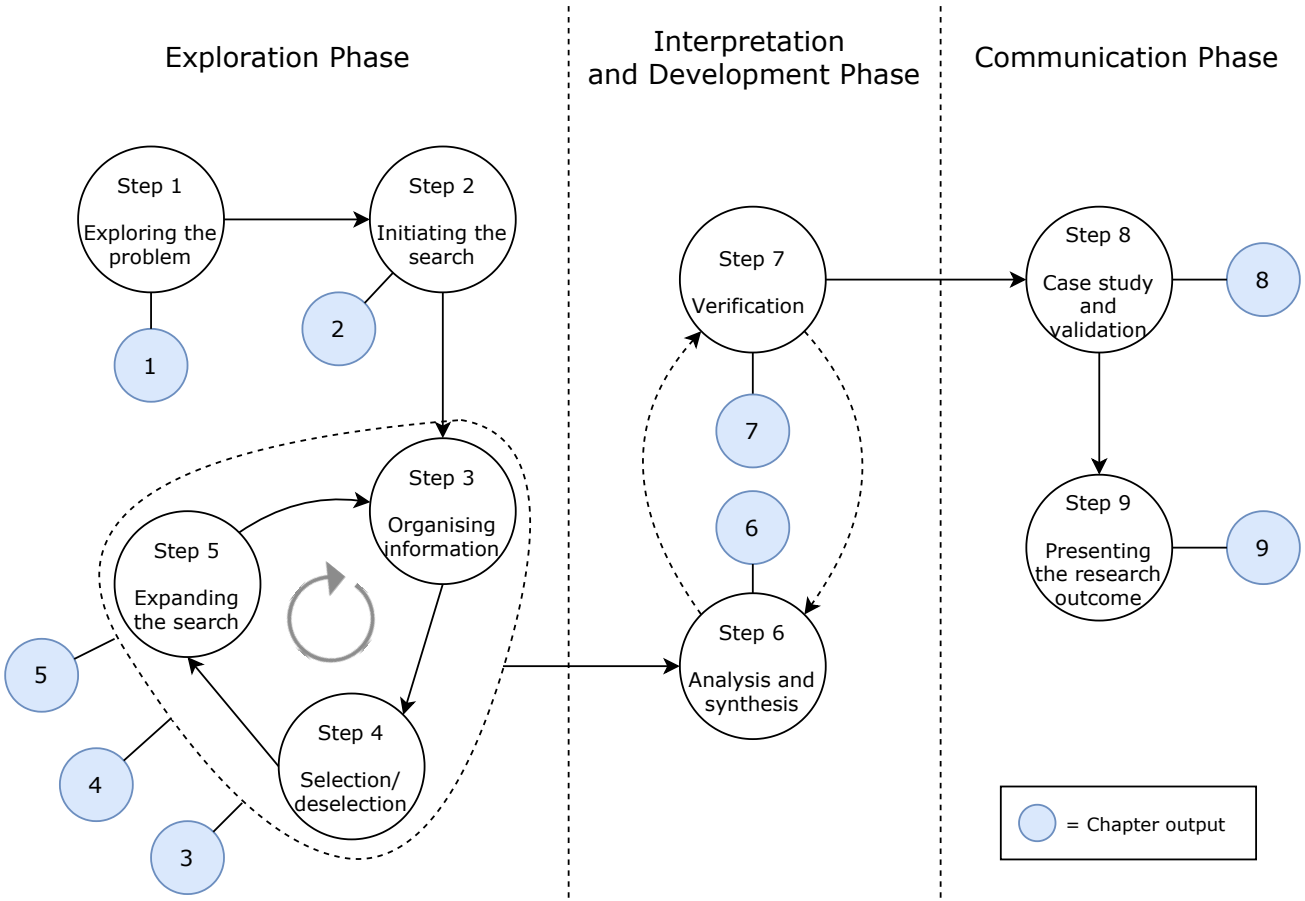

Figure 2.1: Research approach employed in this dissertation. Adapted from Onwuegbuzie *et al.* (2012).

2.4 Research tools and techniques

Research tools and techniques are procedures used to obtain and analyse data.

2.4.1 Self-completion questionnaires

Much like a structured interview, a self-completion questionnaire is one of the main tools used for gathering data using a social survey design (Bryman & Bell, 2015). The use of a self-completion questionnaire in this research, as opposed to structured interviews, was selected as the primary verification technique due to the numerous advantages when comparing the two techniques. Self-completion questionnaires can be constructed to have fewer open ended questions, since closed questions are typically easier to answer. Closed questions are typically easier to understand and therefore reduce the risk that the respondent will fail to understand the question, or inadvertently leave a question unanswered. The shorter nature of questionnaires can also reduce the risk of respondent fatigue. Bryman & Bell (2015) list additional advantages of questionnaires including the rate at which they can be distributed, the absence of interviewer effects and social desirability bias, the lack of interviewer variability, as well as convenience for the respondents. Interviewer effects such as age, ethnicity, and gender, could result in a change of the respondents' behaviour. Social desirability bias is the tendency for people to act in a socially desirable way when an interviewer is present. The negative effects of social desirability bias are well documented (Fisher, 1993).

There are, however, some limitations to the use of self-completion questionnaires. Without the presence of an interviewer the respondent cannot be prompted when experiencing difficulty in answering a question. In addition, respondents cannot be probed by the interviewer to provide additional information when answering questions (Bryman & Bell, 2015). These two disadvantages could result in a greater risk of missing data. In order to avoid this, the self-completion questionnaire must be designed in such a way that it makes answering easy for the respondents.

2.4.2 Case study

Chapter 8 indicates that a well regarded method of ascertaining a maturity model's validity is to deploy the model in a case study with an organisation which is independent from the maturity model's development and testing activities. By implementing the maturity model in such a way, the extent of the model's generalisability can be determined (De Bruin *et al.*, 2005). It is worth noting that in the context of this research and the case study described, the PVR-CMM V2 is not taken through a full implementation cycle. It is acceptable practice to not take a maturity models through it's full implementation cycle in a research context, due

to the lengthy time horizon associated with a full implementation cycle. This characteristic of maturity model development research is demonstrated in a number of doctoral dissertations involving the development of maturity models (Essmann, 2009; Van Dyk, 2013).

The aim of the case study is to determine whether or not the PVR-CMM V2 can indeed achieve it's stated aims. As stated in Section 7.3, the aims of the PVR-CMM V2 are to promote and improve interoperability by addressing the degree of integration of systems involved, to provide guidance on which system components need to be improved, as well as to provide a means for measuring interoperability progress across the community of SRSs in the global PV landscape.

Once an appropriate participating organisation has been identified, the organisation would be contacted and a proposal would be made. If the prospective participating organisation was to accept the proposal, an assessment of their organisation's capability and interoperability maturity would be conducted. After conducting the maturity assessment, the researcher would analyse the results of the assessment and develop a set of practical recommendations with regard to the dimensions that require improvement. These practical recommendations would be delivered to the organisation, along with a validation questionnaire. The validation questionnaire is discussed in detail in Section 9.5.

2.5 Chapter 2: Conclusion

In this chapter, the research methodology was introduced. The research philosophy was described and the pragmatic position adopted was justified. The research approach and strategy were laid out, wherein the relevant research methods were discussed. Finally, the research tools and techniques involved in the verification and validation stages of the research were described and justified.

Chapter 3

Research contextualisation

This chapter focuses on understanding the global PV landscape, what is meant by an interoperable spontaneous reporting system, the challenges and barriers which affect the spontaneous reporting of ADRs, and an analysis of the effects of the lack of standardisation across the global PV reporting system. This chapter concludes with a discussion focussing on the extent to which standardisation and interoperability could alleviate these PV challenges.

The majority of this chapter has been published in the Southern African Journal of Industrial Engineering (SAJIE), in an article titled "An investigation into the value of a standardised global pharmacovigilance reporting system" in November 2017, Vol 28(3) Special Edition, pp 78-88.

3.1 Pharmacovigilance

The terms pharmaceutical drug, therapeutic drug, drug, medicine, and medicinal product are used interchangeably in this dissertation document. A medicinal product as defined by the European Medicines Agency is "any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis" (European Medicines Agency, 2004).

The pharmacodynamics of these drugs on a molecular level are numerous and intricate; and it is resource intensive and difficult to fully characterise the interactions of a drug *in vitro*. The reality is that no therapeutic drug is inherently safe, each treatment situation is unique, and each patient can react differently to a specific treatment.

The Thalidomide disaster of the late 1950's raised concerns around the world with regard to the safety of medicines and the associated dangers of ADRs to public health. In the United Kingdom a medication containing thalidomide was prescribed to pregnant women to treat the symptoms of morning sickness which are associated with the early stages of pregnancy. Initially the drug brought symptomatic relief, however in the months and years that followed, thousands of babies were born with congenital deformities (phocomelia) after *in utero* exposure to the seemingly safe drug. There was a considerable time delay before the causal relationship between thalidomide and phocomelia was identified (World Health Organization, 2002).

It was only in 1968, that the World Health Organisation (WHO) established an International Drug Monitoring Programme (IDMP), with 10 member countries, in direct response to this disaster. The objectives of the IDMP comprised of collecting, processing, analysing and disseminating information pertaining to the safety of medicinal substances. This was the birth of PV.

Considerable research has been conducted in the field of pharmacovigilance since the 1970's, with increasing research outputs generated every year. The majority of the research is generated by and pertains to the North American and European regions.

There is an increasing trend in research into PV activities in developing countries. These countries typically have the more complex and disease burden public health systems, thereby exposing barriers and challenges faced more commonly by developing countries. Olsson *et al.* (2010) investigates some of these challenges and provides useful information for the progress of this proposed research. Developing countries stand to benefit significantly from the collaborative global PV effort, through the leverage of pooled resources and knowledge.

Multiple sources have been identified which point to the need for a standardised reporting system, such as (Barnett, 2015; Field, 2017; Graham *et al.*, 2012; Richesson *et al.*, 2008; Shiffman *et al.*, 2003; Wong *et al.*, 2015). Preliminary findings highlight that the dissemination of knowledge and education of the public are important drivers of ADR reporting adherence. If patients have not been adequately informed, or fail to understand the intended outcomes of their treatment plans, they will be less likely to report any adverse experiences they might have with that treatment plan.

3.2 The process of drug development and approval

To understand how PV reporting methods vary, according to the stage of the drug development process, it is necessary to understand the process of drug development and marketing authorisation. The drug development and approval process according to the Food and Drug

Administration (FDA) of the United States is shown in Figure 3.1. The process of development and approval for new medicines and therapeutic drugs is lengthy and well established. For a medicine or therapeutic drug to gain approval from clinical regulatory bodies and receive marketing authorisation it must meet stringent requirements and pass multiple stages of pre-clinical and clinical trials. Upon completion of these trials, the regulatory body conducts a comprehensive review of the drug in question, with the aim of assessing the potential benefits and harms of the drug.

Once the drug has been approved and marketing authorisation has been granted, the drug may be marketed within the jurisdiction governed by the relevant regulatory body. When the drug is marketed on a global scale the number of patients using the drug can be in the order of millions. This presents an opportunity for a robust global PV system to receive large amounts of data from new patient groups through the spontaneous reporting of ADRs. With a large and multi-ethnic population consuming medications the identification of new drug interactions is made more feasible. Different ethnic groups could respond differently to certain medications due to the effects of Single Nucleotide Polymorphisms (SNPs) which are slight variations in their DNA (Maggo *et al.*, 2016). The consumption of a medication across a large population would also elude to the effects of consuming the medication at varying doses. For a global PV system to be able to draw quantitative conclusions from the data a standard reporting protocol must be established. Currently, problems such as under-reporting and the communication of incomplete, unrepresentative, and uncontrolled data prove to be significant barriers to detecting and characterising new adverse drug interactions and ADRs (Banerjee *et al.*, 2013).

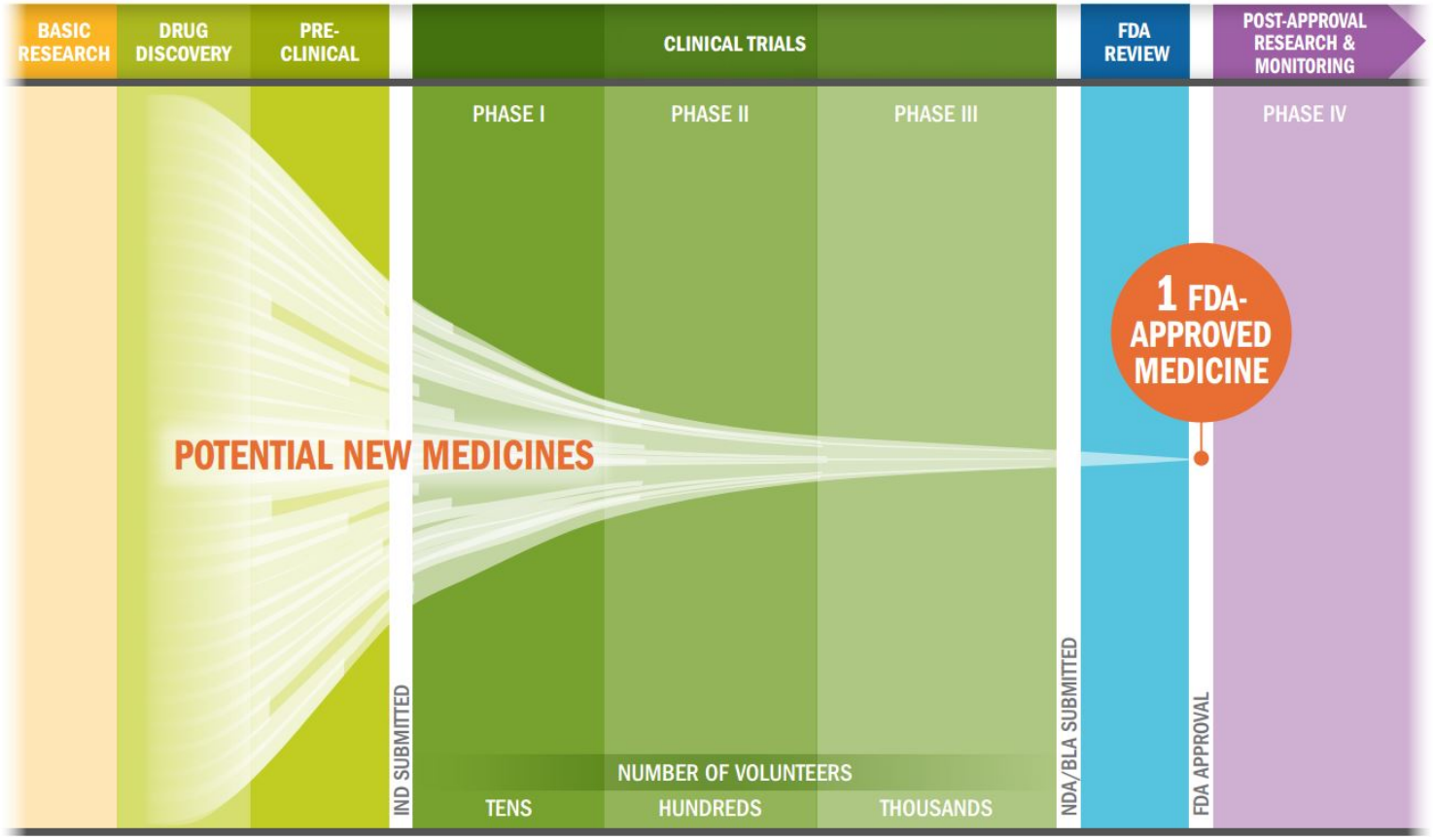

Figure 3.1: Schematic representation of the drug approval process according to the FDA (Pharmaceutical Research and Manufacturers of America, 2018).

3.3 Reporting methods

Data management is a key principle of pharmacovigilance. Sources of data include non-clinical and clinical trials, scientific literature, pharmacoepidemiologic studies, and spontaneous reporting systems. PV reporting systems primarily rely on the generation and detection of signals. A signal is the communication of an ADR or ADE made by a patient, manufacturer or HCP to the appropriate PV centre. The unsolicited reporting, or spontaneous reporting of such ADRs, is the cornerstone of data generation in post-marketing drug safety and surveillance. However, research suggests that spontaneous reporting is not a sufficiently comprehensive method of generating the data that is needed to make quantitative conclusions about the safety of medicines in the long term (Layton & Shakir, 2015; Ndagije *et al.*, 2015; Pal *et al.*, 2013).

There are three primary methods of reporting ADRs and drug safety information, these are Spontaneous Reporting (SR) and two active surveillance methods, Cohort Event Monitoring (CEM) and Targeted Spontaneous Reporting (TSR). In addition to the three methods of reporting, one can also make a broad distinction between a 'pull' and 'push' approach to reporting. Further discussion surrounding this, and the three methods reporting methods can be found in Chapter 4.

3.3.1 Spontaneous Reporting

Spontaneous reporting during the post-marketing phase generates the majority of drug safety data, even more so than the clinical trials during the drug development process (Lester *et al.*, 2013). Lester *et al.* (2013), found that between 52% and 55% of drug label changes were as a result of spontaneous reporting; thereby demonstrating the significance of spontaneous reporting in PV activities. Spontaneous reporting involves the unsolicited generation of a signal by an HCP or a patient relating to the suspicion of an ADR. This method is advantageous over active surveillance methods in that it incurs little to no administrative costs, it covers a large population of potential reporters, as well as a large profile of drugs, and it allows for the monitoring of a medicine throughout its entire life cycle.

3.3.2 Cohort Event Monitoring

Cohort Event Monitoring (CEM) involves the prospective study of the ADRs associated with a specific drug within a small group of patientsa cohort. The primary benefit of CEM is realised when used to observe the effects of a new medicine in the early stages of post-marketing authorisation (Pal *et al.*, 2013). Although all PV activities are centrally focussed on patient

safety, CEM takes the approach of focussing on a specific medication for the time before and during the control period.

3.3.3 Targeted Spontaneous Reporting

Targeted Spontaneous Reporting (TSR) is a methodology which is similar to spontaneous reporting but involves well defined patient groups; where healthcare professionals are on the lookout for specific ADRs (Pal *et al.*, 2013). TSR is an active method of surveillance in a well-defined population group whereas spontaneous reporting is a passive method of surveillance used within an undefined population (Mehta *et al.*, 2014). Being an active surveillance method TSR is therefore more resource intensive when compared to spontaneous reporting, TSR however, produces reporting data of a higher standard. TSR methods have shown strong potential in low- and middle-income countries for the monitoring of drug safety over extended periods of time in populations with specific disease burdens, such as HIV and TB (Pal *et al.*, 2015).

3.4 Standardisation for interoperability

Standardisation is a principle tool used in quality improvement initiatives which focusses on cost reduction and the identification and elimination of inefficiencies within systems (Blind & Mangelsdorf, 2016). The concept of standardisation is broad and spans multiple domains (Xie *et al.*, 2016). The standardisation of a system must be performed by subject matter experts from each of the various domains included in the system; as well as a wide variety of stakeholders who have a vested interest in the system.

Interoperability is defined by the Healthcare Information and Management Systems Society (HIMSS) (2013) as the ability of different information technology systems and software applications to communicate, exchange data, and use the information that has been exchanged. Interoperability enables different health information systems to work together across organisational boundaries to advance the quality of healthcare and improve the efficiency of healthcare delivery.

This chapter aims to drawn a connection between the potential benefits of standardisation for interoperability of reporting systems and the challenges brought about by the fragmented nature of the current global PV context. A review of literature on ADR reporting shows that the traditional method of spontaneous reporting is not effective and is met with a variety of problems such as poor data quality, and insufficient data capturing due to the under-reporting of ADRs by HCPs and patients alike.

3.4.1 Effects of a lack of interoperability

A brief summary of all issues related to the lack of interoperability are presented here. The likely impact of standardisation on the various stages of the PV reporting system will be discussed in the following Sections 3.5 and 3.6. The most wide spread challenge facing PV is a high level of under-reporting (Batel Marques *et al.*, 2016; Graham *et al.*, 2012; Hazell & Shakir, 2006; Koutkias & Jaulent, 2015; Lester *et al.*, 2013), typically attributed to a lack of knowledge, time and incentive (DalPan, 2014; Graham *et al.*, 2012; Hasford *et al.*, 2002), which eludes to the lack of standardised reporting protocols and methodologies. PV is also faced with socio-cultural challenges, such as the existence of a culture of fear surrounding the reporting or ADRs due to a fear of undue disciplinary action taken against HCPs (Hasford *et al.*, 2002; Kim *et al.*, 2010; Suku *et al.*, 2015).

The literature also highlights the urgent need for educational awareness of PV activities and the simplification of the ADR reporting process to improve public participation (Bhagavathula *et al.*, 2016; Layton & Shakir, 2015; Sevene *et al.*, 2008; Stergiopoulos *et al.*, 2016). Accountability among all stakeholders in a health system is important for the overall successful functioning of the system. A systematic review of ADR reporting systems by Bailey *et al.* (2016) found a high degree of variability, with 1782 distinct data elements having been identified across 108 systems; thus, showing the need for ADR report forms to consist of standardised terminology and a comprehensive set of unique data elements.

3.4.2 What is meant by an interoperable reporting system

Given the scope of this research, an interoperable reporting system is envisioned to comprise of the following characteristics:

- A global system wherein an ADR is reported once, with data of high quality to facilitate causality analysis;
- A transparent system where data is accessible by all stakeholders, this includes public health programs (PHPs), regulatory authorities (RAs), manufacturers, HCPs, patients, and the public at large;
- A system which ensures the confidentiality of patients;
- A system which reduces fragmentation and duplication of data and resources;
- A system which improves resource utilization in resource limited contexts;
- A system which reduces administrative pressure, allowing HCPs to direct their attention to other priorities and give them more time to report ADRs; and

- A system which enables HCPs to make more informed therapeutic decisions and improve patient safety.

The objectives of this system would be:

- To reduce the frequency and severity of ADRs by widening the scope of pharmacovigilance on a global level;
- To improve causality analysis and risk assessment, allowing HCPs to make more informed therapeutic decisions;
- Enabling quantitative conclusions to be made regarding the safety of medicines over long term use; and
- To improve the communication of drug safety information between HCPs and patients.

3.5 Analysis of the effects of the lack of an interoperable global PV reporting system

ADRs are a significant cause of morbidity, mortality and increasing costs for PHPs (Nazer *et al.*, 2013). By facilitating the communication and collation of comprehensive ADR data, the objectives of PV reporting can be achieved. These objectives include the characterisation of known reactions, to measure risk, to identify new reactions by the detection of signals, to characterise drug interactions, to identify risk factors such as age, gender, dosage etc.; to assess safety in various patient groups (pregnancy, elderly, paediatric, etc.), and to detect and measure the inefficacy of medicines.

Data pooling has a direct effect on the accuracy of ADR frequency estimation. By not pooling data from across the international landscape, we lessen the rate of detection of rare but clinically significant ADRs (Olsson, 1998), specifically those which occur with low incidence rate but can pose a significant threat to public and patient safety. By pooling data, these silent but serious ADRs can be more readily detected.

Patel *et al.* (2017), found that the mean preventable ADRs leading to hospitalisation was 45.11%, with the primary suspects being cardiovascular system drugs (28.1%), non steroidal anti-inflammatory drugs (NSAIDs) (16.1%), nervous system drugs (16.9%) and musculoskeletal drugs (16.1%). Inappropriate drug selection due to a misdiagnosis, toxic drug serum levels, and failure to predict and avoid known drug interactions are among the leading causes of preventable ADRs.

3.5 Analysis of the effects of the lack of an interoperable global PV reporting system

Stages of PV system / *Challenges*	ADR reporting	Data collation	Causality analysis	Risk assessment	Decision-making	Appropriate action	Evaluation of outcomes
Under-reporting	x						
Partnerships	x	x	x	x	x	x	x
Culture and transparency	x	x	x	x	x	x	x
Public participation	x					x	x
Quality reports of ADR reports		x	x	x			
Text-mining		x	x	x			
Lack of data	x	x	x	x			
Causality analysis			x	x			
Proactive vs reactive systems	x					x	
Lack of PV centres		x			x	x	x
Insufficient resources	x	x	x	x	x	x	x
Lack of reporter feedback					x		
Clinical trials		x	x	x			
Country specific factors	x	x	x	x	x	x	x

Potential for standardization to alleviate PV challenge

High — Low

Figure 3.2: Breakdown of challenges facing different stages of the PV system. Adapted from Lamprecht *et al.* (2017).

There exist a multitude of complex challenges which hinder PV activities, Figure 3.2 shows the Lamprecht *et al.* (2017) breakdown of the challenges and which part of the PV system they are associated with. The colour grading scale shows the extent to which a standardised ADR reporting system would alleviate the respective challenges and has been added to the matrix as part of this research on the value of standardising ADR reporting. The colour gradings are motivated in the subsections below.

It is important to consider the limitations of spontaneous reporting systems. Due to the unsolicited nature of spontaneous reporting, problems such as under-reporting, the inability to derive incidence and prevalence rates due to the lack of denominator data, and the potential for reports to contain insufficient clinical data are widespread.

3.5.1 Under-reporting

Under-reporting is widely regarded as the most prominent challenge across the PV landscape. This issue has been brought to the fore by various journal publications, such as (Alvarez-Requejo *et al.*, 1998; Bäckström *et al.*, 2004; Bhagavathula *et al.*, 2016; Hazell & Shakir, 2006; Moride *et al.*, 1997; Neubert *et al.*, 2013).

A systematic review performed by Hazell & Shakir (2006), provided evidence of widespread under-reporting across 12 countries, stating that the rate of under-reporting was as high as 94%. The notion of under-reporting in the literature has often been attributed to the knowledge, attitudes and practices (Bhagavathula *et al.*, 2016) of HCPs. Common concerns and barriers to reporting of HCPs have been identified, these include lack of knowledge of the functioning of a PV system, lack of incentive to report ADRs, lack of time, and interestingly, a fear of blame (Kim *et al.*, 2010). HCPs, particularly in low income countries have been found to show a reluctance in reporting ADRs as they believe it reflects poorly on their professional ability to treat their patients (Graham *et al.*, 2012). An interoperable and standardised reporting system would assist in reinstating confidence in both HCPs and patients by ensuring confidentiality of submitted reports.

Through standardisation of the PV reporting system and associated protocols, PV in general will become easier and more manageable to include in all undergraduate training curricula of HCPs. The concept of a minimum requirement report is worth further investigation. This form would seek to capture the most important characteristics of the ADR, the medication, and the patient. If a more detailed follow up report must be filed, the HCP and the patient would be notified accordingly. HCPs often cite a lack of time as a primary reason for not filling out ADR reports, a minimum requirement form would be less time consuming to complete and could therefore improve under-reporting rates.

A further improvement would be the use of a feedback mechanism to provide the HCP and patient with acknowledgement of receipt of the ADR report. The provision of feedback to reporters of ADRs would almost certainly increase the overall rate of spontaneous reporting among HCPs and patients alike. This feedback could comprise of a simple acknowledgement of receipt or could provide information to the reporter regarding an appropriate course of action to take in order to treat the symptoms of the ADR which are experienced by the patient.

3.5.2 Culture and transparency

There exists a need for a change in culture and transparency surrounding ADR reporting (Chruscicki *et al.*, 2016). There is a misconception among many healthcare practitioners, particularly those in low- and middle-income countries (Bhagavathula *et al.*, 2016; World

Health Organization, 2006), that PV is not the responsibility of a public health program, but rather that of the pharmaceutical industry itself. Transparency is improving in PV systems around the globe with some countries such as Canada and the Netherlands making their spontaneous reporting databases freely accessible by the public (Molokhia *et al.*, 2009). It is important to understand the distinction between transparency and confidentiality, and how they do not necessarily contradict one another.

Transparency of the system would enable all stakeholders to interact with the system and extract all the ADR data that pertains to their role in the PV system. Confidentiality of patient information can be achieved by not disclosing information to unauthorised parties. In the PV context, there are certain elements of an ADR report which should be disclosed to all stakeholders, but also some which contain sensitive information about the patient. By ensuring the anonymity of patients, when sharing their ADR report data, they can have confidence that the data which they generate will not be used against them by any third-party entities.

Interoperability as a product of standardisation would improve transparency of the system and improve accessibility of up-to-date information regarding the safety of medicines. Improving accessibility to the latest information would allow for patients to have a greater degree of confidence in their PHP. Accountability can be improved through improving the knowledge, attitudes and practices of HCPs during their undergraduate training. When HCPs understand that the responsibility of PV is shared across all stakeholders in the health system, they will be able to report ADRs with confidence that their actions will not result in undue disciplinary action taken against them.

3.5.3 Public participation

Patient-centricity is a key aspect of an effective PV system. Through fostering an environment wherein, the patient is well informed and confident, public participation is likely to improve. PHPs need to provide accurate and transparent information to the public to gain public trust, a notable example of this would be with national immunization programs. For the public to cooperate with a national program for immunization, the risks and benefits of the program must be adequately communicated.

An electronic web-based form should be made available to all members of the health system, and could be available in all languages to improve ease of use. The use of a feedback mechanism to provide HCPs and patients with acknowledgement of receipt of their ADR report would likely improve levels of reporting. People will be more likely to participate in the system when they are made to feel valued by the system. Giving the patient a platform to make their voice heard and acknowledging their report is an important step in improving public participation. The

encouragement of patient reporting would increase the rate of overall spontaneous reporting and would likely enable earlier detection of unexpected ADRs (Jarernsiripornkul *et al.*, 2017).

3.5.4 Lack of data

The development of a standardised and interoperable ADR spontaneous reporting framework would directly support the WHO's efforts to manage PV activities on a global scale. An effective ADR spontaneous reporting system would allow for the early detection of ADRs in the post-marketing phase. Incidence rates of the ADRs could be established, and the identification and characterisation of novel drug interactions could take place. Bailey *et al.* (2016), found a high degree of variability among the 108 reporting systems in their study, they also point to the lack of standardised data elements in reporting forms, having identified 1782 distinct data elements, which were mapped to 33 reporting concepts. A standardised reporting form would comprise of a comprehensive list of unique data elements, thereby prompting the extraction of all demographically and clinically relevant data relating to the patient and the ADR.

This reduction in the number of data elements can be achieved through the use of standardised terminology. The two principal medical terminology directories are the MedDRA (Medical Dictionary for Regulatory Activities) and the WHO-ART (World Health Organisation Adverse Reactions Terminology) dictionaries. Discrepancies between MedDRA and WHO-ART contribute to the problem of data quality. An interoperable spontaneous reporting system would allow for improved causality analysis through the pooling of uniform data, extracted from various databases using standardised terminologies.

3.5.5 Proactive vs. reactive system

The unsolicited nature of spontaneous reporting makes it a reactive system. With 55% of all drug label changes in the United States since 2010 being in direct response to spontaneous reporting of ADRs (Lester *et al.*, 2013) it is clear to see that an improved reporting system can benefit the proactive drug safety activities such as drug labelling and package inserts. By improving efficiency in ADR reporting, drug safety labels will reflect the latest safety information, thereby allowing HCPs to make more informed therapeutic decisions.

3.5.6 Lack of PV centres and insufficient resources

Healthcare systems are unique to the countries in which they function. PV activities, particularly in low- and middle-income countries (LMIC) are often considered 'nice to have' and take second place to efforts focussed primarily on improving access to medicines (Olsson *et al.*, 2015). Given the variety and complexity of public healthcare programmes around the world, *the* UMC faces considerable challenges and difficulties in attempting to co-ordinate the IDMP.

A study by (Olsson *et al.*, 2010), found that only 41% of the countries studied had any form of budget allocated to PV.

The lack of standardisation and interoperability results in reporting systems receiving reports with incomplete or insufficient data, thereby placing stress on the system and diverting resources such as time, people and money, away from other more important activities (DalPan, 2014). Accurately quantifying the cost of health care is difficult enough on a national public health program level, assessing the costs associated with ADRs on a global level is even more challenging. However, research has been conducted to expose the reasons for these costs as well as to give estimates of the costs incurred by PHPs.

Costs associated with ADRs are attributed to the extended lengths of hospitalisation, the costs of treating illnesses caused by ADRs and the cost of avoiding ADRs. The majority of the literature on the pharmacoeconomic aspects of ADRs focus primarily on costs due to the hospitalisation of patients due to ADRs. A 1998 study found that complications brought on from ADRs account for the fourth to sixth leading cause of death in hospitalised patients in the United States of America (Lazarou *et al.*, 1998). Total hospital costs associated with ADRs in the US have been estimated to be between $30 billion and as high as $130 billion annually.

By pooling resources among PHPs and drug manufacturers, a mechanism could be established to facilitate the follow-up of minimum requirement reports that have been received, as required. If sufficient minimum requirement reports, at an aggregate level, generate a signal which eludes to the presence of an unexpected ADR, then the appropriate resources can be allocated for a more thorough investigation into the safety of a specific medicine, such as a CEM initiative.

3.6 The potential impact of interoperability

Pharmacovigilance activities contribute to the prevention of unnecessary patient harm, improved clinical practices, and support research and education activities. Patient safety remains the central focus among all PV activities; with the end goal of assisting HCPs in making more informed therapeutic decisions for their patients. In order to identify and characterise evidence-based causal relationships between ADRs and their suspected medicines, standardised data must be communicated efficiently and effectively along all stages of the PV system.

An effective, interoperable ADR spontaneous reporting system, would allow for the early detection of ADRs in the post-marketing phase. Incidence rates of the ADRs could be established, and the identification and characterisation of novel drug interactions could take place. PV activities contribute to the prevention of unnecessary patient harm, improved clinical practices, and support research and education activities. The advantages of spontaneous reporting over active surveillance are well defined in literature. Spontaneous reporting is less expensive and

less labour intensive when compared to an active surveillance approach. Spontaneous reporting is administratively simpler and allows for continuous passive monitoring of medicinal products.

The development of an interoperable ADR spontaneous reporting framework would directly support the WHO's efforts to manage PV activities on a global scale. If regional differences are insuperable or a universal solution found to be infeasible, the sharing of best practices, together with the leveraging of PV capacity and capability through collaboration and partnership must be considered. Governments and their respective regulatory bodies need to provide political mandate to the relevant role players, together with supporting legislation and standard operating procedures (SOPs) to improve awareness of and adherence to good PV practices across all levels of their public health programs (PHPs).

A collaborative global effort is needed to fast track PV development around the world. It is those countries that do not have the necessary facilities, expertise and resources for PV that need them the most (World Health Organization, 2006). Developing countries often have the highest disease burden on their PHPs. The strength of global PV lies in the integration of various national PV systems. Although efforts may have been made to standardise parts of the PV system, the focus must shift to the diffusion and successful adoption and implementation of those standards.

3.7 Chapter 2: Conclusion

This chapter described the global PV landscape, what is meant by an interoperable spontaneous reporting system, the challenges and barriers which affect the spontaneous reporting of ADRs, and an analysis of the effects of the lack of interoperability across the global PV reporting system. The chapter concludes with a discussion focussing on the extent to which standardisation for interoperability could alleviate these PV challenges.

Chapter 4

Reporting of adverse drug reactions

This chapter describes the flow of information through the PV system, the key role players in the system, as well as the communication channels between the key role players in the PV system. The different methods for reporting ADRs are discussed and the current best practices are described. A comparison between methods currently in use by 3 selected countries is made and a comparative analysis is performed, outlining their respective differences and discrepancies. The introduction of the Electronic Health Record (EHR) as a disruptive technological innovation is discussed and a new approach to addressing the challenges of under-reporting is introduced. The concept of maturity models are introduced as a means of addressing the challenges facing ADR reporting, regulatory compliance, and general population health and safety within the PV context.

4.1 Introduction

The effective use of a strong PV system ensures continuous worldwide safety and efficacy monitoring. For effective PV to take place we need to ensure that all key role players contribute to PV reporting and the effective communication of information.

4.1.1 Who are the respective role players?

The PV framework relating people, functions, structures, and expected outcomes and impacts can be seen in Figure 4.1. Generally the reporting of an ADR begins with a patient who experiences the ADR and culminates in the relevant information being effectively communicated to a national PV centre as well as *the* Uppsala Monitoring Centre, where it can be analysed and where the outcome of this analysis can be taken into consideration for the necessary decision-making processes. The final step in improving patient safety is in disseminating the information back down the chain of communication towards the patient. It is important to distinguish between a reporter and a sender. A reporter is someone who reports the facts

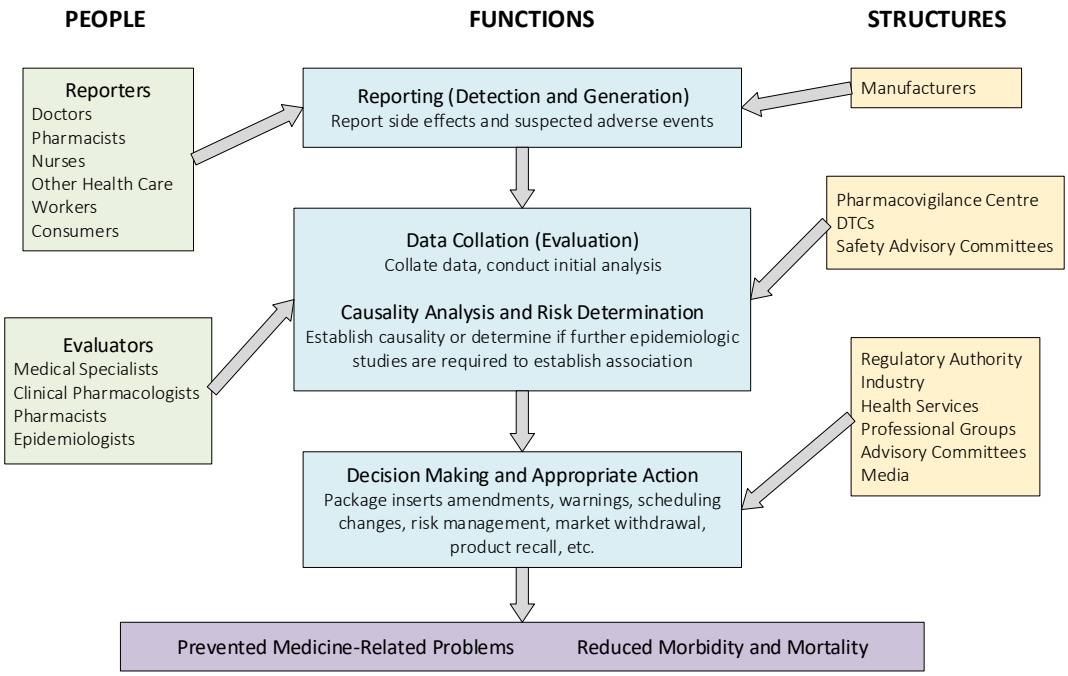

Figure 4.1: The pharmacovigilance framework relating people, functions, structures, and expected outcomes and impacts (Strengthening Pharmaceutical Systems (SPS) Program, 2011).

related to an ADR, this is usually the patient themselves or a HCP in consultation with the patient. A sender is simply a secondary source of reporting who transmits the information from one role play to another, for example a Marketing Authorisation Holder[1] (MAH) and the regulatory authority. The role players involved in the reporting of ADRs are described below.

1. **Patients/Consumers**: Generally the process of reporting an ADR is initiated by the patient who has experienced the ADR. In countries which restrict the reporting of ADRs to HCPs only (i.e. where patients are not permitted to report ADRs to PV authorities directly), the report is made up of an interpretation of the description originally provided by the patient, together with some objective measurements. The patient communicates with his or her HCP and thus the initiation of a spontaneous ADR report occurs. In this case the responsibility rests with the HCP to ensure that the report is transmitted to the necessary PV authority. Most countries had restricted the reporting of ADRs to PV authorities to HCPs, only since the 2000's did it become more common to allow for patients to report directly to PV authorities (Herxheimer *et al.*, 2010). Inácio *et al.* (2017) performed a systematic review of literature on patient reporting wherein the advantages

[1] A Marketing Authorisation Holder is a person or entity who has received the right to market and sell a medicinal product within the jurisdiction of the regulatory authority which awarded the marketing authorisation.

and limitations of patient reporting were summarised. Key advantages include the faster accumulation of information which complements the information received from HCPs, as well as more detailed information found in the patient reports. The limitations of patient reporting include patients questioning the validity of their judgement on ADRs, as well as a low level of awareness among patients of the availability of patient reporting. Inácio *et al.* (2017) concluded that "patient reporting of ADRs provides new information and perspective in a way otherwise unavailable".

In 2012 the European Union PV system underwent major regulatory reform, with the introduction of the legal right for citizens to report suspected ADRs directly to national PV centres (Borg *et al.*, 2011; Steurbaut & Hanssens, 2014). According to the 2016 annual report of the European Medicines Agency (2016a), 2015 saw an increase of 30% in patient reporting with 48 782 patient reports, compared to the 37 797 reports in 2014. The United Kingdom has allowed patient reporting of ADRs since 2005, however a study by Avery *et al.* (2011) found that in 2011 only 8,5% of patients were aware of the possibility of reporting.

2. **Health Care Professional**: The responsibility to report ADRs traditionally rested with physicians, however in recent years there has been a trend in which the responsibility to report ADRs is shared among all HCPs including doctors, pharmacists, nurses, other healthcare workers and carers. It is well known that the success of any spontaneous reporting system depends on the active engagement of reporters. By restricting reporting to only physicians it was thought that the reports would contain data of higher quality. A review of ADR reports by Hornbuckle *et al.* (1999) argues that by allowing reporting by different HCPs across the healthcare setting, different kinds of drug related problems would be uncovered. Wherever medicines are being consumed, in which ever health setting including public and private hospitals, doctors practices, nursing homes, clinics, pharmacies etc., there should be an awareness of ADR reporting and the capacity to report these events to the necessary PV authorities. By inviting all HCPs to report ADRs, a full spectrum of the complications associated with medicines can be achieved (Hornbuckle *et al.*, 1999). After the consultation with the patient, the HCP will examine the possible causes of the ADR. Possible causes include (*the* Uppsala Monitoring Centre, 2018e):

    - The possibility of a misdiagnosis,
    - Interactions with other medications, foods or substances,
    - Non-adherence to the dosing instructions of the medication, or

- The source or quality of the medication (falsified or sub-standard, out of specification medication).

The HCP initiates the formal process of reporting the ADR to their regional or national PV centre, this is the first step towards the creation of an Individual Case Safety Report (ICSR). An ICSR is compiled at the national PV centre, where the necessary information can be solicited from the HCP and the patient experiencing the ADR. This process can involve multiple back and forth communications between all three role players.

3. **Hospitals and Academia**: The role of Hospitals and Academia in the reporting process is somewhat limited in that HCPs report directly to the national PV centre. The primary role of the hospital in the reporting of ADRs is to provide the HCPs operating within it, the necessary knowledge and tools to report ADRs. This role is often delivered through a drug and therapeutics committee (DTC). The American Society of Hospital Pharmacists provides the following definition for a DTC: "The committee that evaluates the clinical use of medicines, develops policies for managing pharmaceutical use and administration, and manages the formulary system[1]" (American Society of Health-System Pharmacists, 2008). A DTC is formally organised group of HCPs which can include medical specialists, clinical pharmacologists, pharmacists and epidemiologists. The existence and opreation of a DTC is considered one of the WHO's 22 prerequisites for a functioning PV system (World Health Organization, 2010). The primary function of the DTC is, among other things, to manage ADRs and medication errors, thereby decreasing the amount of ADRs occurring. The benefits of a properly functioning hospital DTC include increased staff and patient awareness of ADR reporting, as well as improved quality of patient care and health outcomes. A DTC should have an appropriate plan in place to address problems associated with ADRs including regular monitoring, assessment, reporting, and prevention. DTCs contribute to drug quality assurance through facilitating communication among all the various role players in the health facility as well as through communication with manufacturers and regulatory authorities.

4. **Regional and national PV centres (National competent authorities)**: Every member state of the WHO's programme for International Drug Monitoring must set up a national PV centre which has the necessary designated staff, stable funding, clear mandates, and well defined structures and roles. These national PV centres must also ensure the existence of a national ADR reporting form, as well as a national database which supports the management of the ADR reports (Maigetter *et al.*, 2015).

[1] Formulary - A list of medicines that are approved for use in the healthcare system by authorised prescribers.

It is at the regional or national level that spontaneous reports of ADRs are collated and aggregated together to be subjected to various analyses. The national PV centres of member countries of the PIDM are encouraged to submit ICSRs to *the* UMC's VigiBase as early as possible or at least on a quarterly basis (*the* Uppsala Monitoring Centre, 2018e).

Regulatory authority: Regulatory authorities (RAs) are government structures which are responsible for the scientific evaluation, supervision and safety monitoring of pharmaceutical products in their area of jurisdiction. In South Africa this is performed by the South African Health Products Regulatory Authority (SAHPRA) which evolved from and is based on the Medicines Countrol Council (MCC). Undoubtedly the most recognisable role players in the the PV landscape from the perspective of the general public would be the United States Food and Drug Administration (FDA) and its European counter-part the European Medicines Agency (EMA). These are the two largest pharmaceutical regulatory bodies in the world. RAs operate in terms of the laws and regulations prescribed to them by their respective Departments of Health. In South Africa this is the Medicines and Related Substances Act, 1965 (Act 101 of 1965). It is worth noting that both the FDA and EMA have their own electronic ADR processing and management systems. The FDA provides those within its jurisdiction to report ADRs via the FAERS (FDA Adverse Event Reporting System), this system makes use of standards which enable interoperability of information with the VigiBase database. Similarly the EMA, on behalf of the EU, provides its inhabitants with the EudraVigilance system, which operates within the European Economic Area (EEA). EudraVigilance also supports the standards in use by *the* UMC's VigiBase.

Pharmacovigilance Risk Assessment Committee (PRAC): The European Medicines Agency (EMA) has a specialised team which is mandated to perform PV risk management related tasks, the Pharmacovigilance Risk Assessment Committee. The PRAC is responsible for the design and evaluation of post-authorisation safety studies, as well as PV auditing in the EU.

5. **The World Health Organisation**: The Quality Assurance and Safety: Medicines team of the WHO operates within the Department of Essential Drugs and Medicines Policy, under the cluster of WHO Health Technology and Pharmaceuticals. The goal of the team is to ensure equity of access to essential drugs, drug quality and safety, and the rational use of drugs.

Uppsala Monitoring Centre (UMC): *The* UMC is the organisation charged with the management of an international database of ADR reports received from the national PV centres of countries belonging to the Programme for International Drug Monitoring (PIDM). *The* UMC actively promotes the international use of the Individual Case Safety Report (ICSR) standard exchange format, the International Conference on Harmonization E2B (ICH E2B) (Lindquist, 2008). *The* UMC has developed a set of software tools and methods for the communication of PV data. The software tools and methods which facilitate the management of PV data, are collectively referred to as the "Vigi tools and methods"[1].

6. **MAHs and Pharmaceutical Industry**: MAHs and manufacturers are subjected to different rules and regulations depending on the country which they are marketing their medicines in. Generally the MAHs are required to operate and maintain a spontaneous reporting system, however, these often differ from the national PV centre's reporting systems. The MAH must follow the guidelines set by the government that is regulating its operations. For example the European Medicines Agency, of the European Parliament. In countries where patient reporting is permitted but the PV centre is not part of a regulatory body, the exchange of patient report information with pharmaceutical companies must be carefully considered.

7. **Media**: The media plays an important role in alerting the public whenever an acute problem with a medication arises. It is for this reason that a good relationship must be maintained between those in charge of PV activities and journalists. Pharmacovigilance data is understood differently by HCPs compared to consumers. For this reason, to create successful communication with the public, the type of information, level of detail and the communication channel used, must all be carefully considered.

8. **Professional Groups**: Professional medical and pharmaceutical groups should seek to reinforce that patient reporting by no means replaces the need for reporting by HCPs. These groups and organisations must encourage their members to take initiative and continue to increase the number of reported ADRs.

[1]The tools include VigiBase, VigiLyze, VigiAccess, and VigiFlow; while the methods include vigiGrade, vigiMatch, vigiPoint, vigiTrace, and vigiRank (*the* Uppsala Monitoring Centre, 2018b). These tools and methods are discussed in more detail in Section 4.4.

4.1.2 The flow of information

The successful operation of a PV system is dependent on the successful communication of relevant ADR information from the patient experiencing the ADR to the relevant PV authority, so that the necessary action can be taken, in a timely manner, so as to prevent medicine related problems and reduce morbidity and mortality associated with ADRs. Reporting or the detection of ADRs and subsequent generation of ADR data is therefore a critical function in the PV system (see Figure 4.1). The communication channels used during the reporting of ADRs is depicted in Figure 4.2, while the types of interaction amongst the various role players in PV reporting is characterised in Table 4.1. As is evident, there exist a multitude of communication channels which are involved during the reporting of ADRs.

In the event of a patient experiencing an ADR from the consumption of a medicine, the reporting process can be initiated in one of two ways, by consulting with a relevant HCP (typically a doctor, a pharmacist or a nurse) or, depending on where the patient lives and the severity of the ADR, direct patient reporting to a regional or national PV centre. The patient and their HCP discuss the ADR and investigate possible causes of the ADR. These causes can include a misdiagnosis, an interaction between the prescribed medicine and another medicine or food substance, an error relating to the administration of the medicine or failure to adhere to the dosing and scheduling instructions of the medicine, or the possibility of the medicine being counterfeit or of sub-standard quality. A decision is reached by the patient and the HCP in terms of how to proceed with the treatment of the ADR (feedback), this could include a change in medication, a change in dosage or a change in frequency. This decision is often reached through the collaborative decision-making efforts of multiple healthcare professionals (see cell B2, in Table 4.1), each with unique knowledge bases, across multiple healthcare disciplines. At this point, in an ideal situation, regardless of the severity, duration or outcome of the ADR, the HCP would initiate a spontaneous report of the ADR to the relevant PV authority such as a regional or national PV centre.

Table 4.1: Characterising the types of communication between different role players involved in PV reporting.

		Patient	HCP	DTC	Regional PV Centre	National PV Centre	MAH	UMC
A	Patient	-		-	-			-
B	HCP							-
C	DTC	-		-			-	-
D	Regional PV Centre	-					-	-
E	National PV Centre							
F	MAH			-	-		-	-
G	UMC			-	-			-
		1	2	3	4	5	6	7

 = Report propagated/transmitted forwards.

 = Private system involved.

 = Feedback provided in some form.

 = Payment required.

 = Legal/Regulatory aspect.

 = Collaboration.

- = No or little interaction.

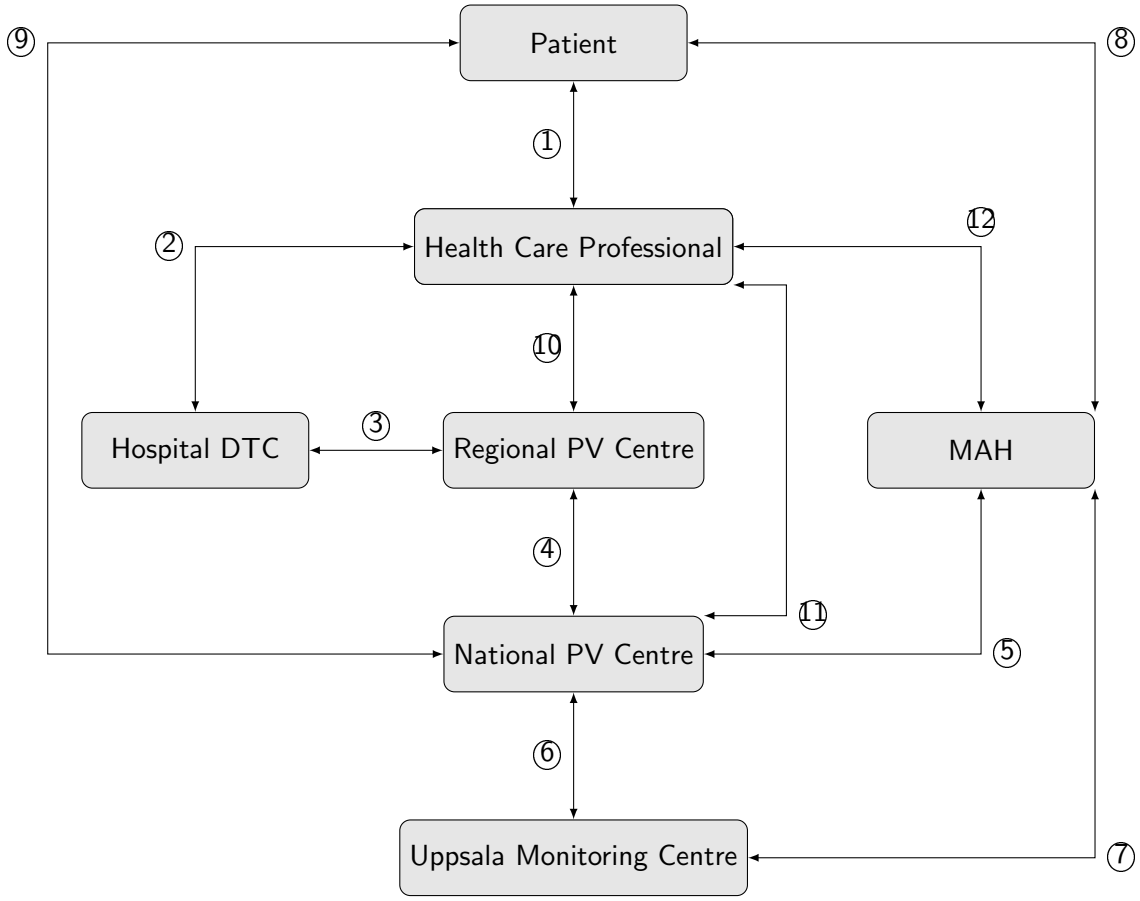

Figure 4.2: A schematic representation of the communication channels used during the reporting of ADRs.

Row A in Table 4.1 shows the different interactions that take place between the patient and the other role players in PV. A study by Saleh *et al.* (2018) found that 44 countries allow for direct patient reporting of ADRs to national PV centres (see cell A5, in Table 4.1). This is largely due to the launch of the eReporting module of *the* UMC's VigiFlow system[1] in 2014, which is free to use for all member countries of the WHO IMDP (*the* Uppsala Monitoring Centre, 2018c). Many of the most prominent pharmaceutical companies or MAHs have their own proprietary systems (see cell A6, in Table 4.1) for capturing data on ADRs experienced by their customers. The reason that these systems differ to the system in use by the country in which the MAH markets their products is that the MAH operates in multiple countries and is subject to different laws and regulations. MAHs and national PV centres have different interests when it comes to collecting information on ADRs, national PV centres aim to protect and promote public health, while MAHs seek to gain an improved understanding of the marketability of their pharmaceutical products. It is important to note that member countries of the WHO PIDM

[1] A web-based ICSR management system.

do require all MAHs operating within their jurisdiction to submit all ADR reports that they might receive to the relevant PV authority, which in most cases is the national PV centre. For the purpose of this research, we will consider that any ADR reporting performed via an MAH's proprietary system is supplementary to the reports of ADRs which are transmitted between the reporters and the national PV centres.

In some cases, the HCP will be a member of, or interact with, a Drug and Therapeutics Committee (DTC) within the healthcare facility in which they operate (see cell B3, in Table 4.1). The DTC might provide initial feedback to the HCP in terms of how to proceed with treating the patient. The DTC would have somebody responsible for PV activities and would be able to provide support to HCPs when it comes to initiating the ADR report to the regional or national PV centre. The DTC will also keep a record of all the ADRs occurring within the healthcare facility and can adjust the facility's formulary as necessary if required. If a regional PV centre exists, then the HCP will initiate the ADR report to the regional PV centre via the healthcare facility DTC. If no DTC or regional PV centre exists, then the HCP will report the ADR directly to the national PV centre. Depending on the country in question and the availability of resources for PV activities, the reporting of ADRs to this point (the National ICSR database) can occur via a number of formats such as paper-based forms, facsimiles, e-mail, telephonic, text messaging, online forms, patient record systems, or mobile applications. Nigeria for example makes use of the PRASCOR system (Pharmacovigilance Rapid Alert System for Consumer Reporting), a short code service for consumers to alert the National Agency for Food and Drug Administration and Control (NAFDAC) of safety or quality issues via SMS. When a reporter makes use of this system, the national PV centre in Nigeria phones the reporter to provide feedback and if necessary request additional information pertaining to the ADR (The Nigerian National Agency for Food and Drug Administration and Control, 2018).

In the case of the European Union, one could consider the national PV centre of the EU member states as regional PV centres which operate under the guidance of the European Union's regulatory authority, the EMA. Similarly in the United States the regional PV centres within each of the states fall under the jurisdiction of the FDA.

The majority of the challenges in PV which were discussed in Chapter 3 are generally contained within the PV system in the stages leading up to the generation of an Individual Case Safety Report (ICSR), after which the system for the transmission of ADR information is largely standardised. These challenges include under-reporting due to poor knowledge, attitude and practices (Bhagavathula *et al.*, 2016); and a lack of financial incentive (Kim *et al.*, 2010). Further challenges include poor culture and transparency in PV, low public participation, insufficient resources, and a lack of data.

Figure 4.3 shows what can be considered as the 'ideal' pathway for the reporting of ADRs. Reporting is initiated upon consultation between the patient experiencing the ADR and their HCP. In an ideal situation the patient would be able to report the ADR directly to the national PV centre via a direct patient reporting mechanism. A study by Saleh *et al.* (2018) found that 44 countries of the WHO PIDM allow for direct patient reporting. The benefits of direct patient reporting are frequently discussed in literature, with the consensus that direct patient reporting of ADRs yields more detailed information about how the ADR affects a patient's quality of life. Direct patient reporting has also been identified as an important tool for assessing the effects of a pharmaceutical product throughout its entire life cycle, as evidence has shown that most HCPs are reluctant to report ADRs from medicines which have existed on the market for a number of years prior to the ADR taking place (Agarwal *et al.*, 2013).

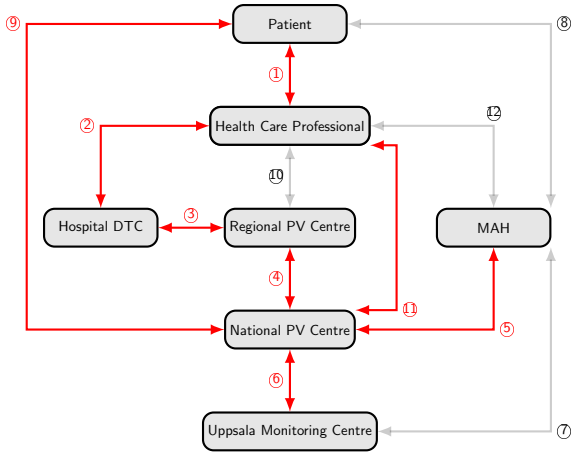

Figure 4.3: A schematic representation of the 'ideal' communication channels used during the reporting of ADRs.

In Figure 4.3 the information moves in a linear fashion from the patient to the HCP (Flow 1, in Figure 4.3), the DTC (Flow 2, in Figure 4.3), a regional PV centre (Flow 3, in Figure 4.3), and finally a national PV centre (Flow 4, in Figure 4.3). It is at the national PV centre where the information is translated from one of several types of reporting media (paper-based form, fax, telephone, etc.) into a standardised electronic format known as an Individual Case Safety Report (ICSR) (see Section 4.3). Member countries of the PIDM can make use of *the* UMC's VigiFlow software to capture the data and compile an ICSR. The compilation of an ICSR can consist of multiple instances of data entry, this might be necessary in the case that the national PV centre solicits additional information from either the patient or the HCP in order to compile a more comprehensive ICSR. Once the ICSR has been formalised the national PV centre sends the ICSR to the MAH and *the* UMC simultaneously (see cells E6 and E7, in Table 4.1)(Flows 5 and 6, in Figure 4.3).

In terms of the MAHs communication with other role players, their proprietary systems could provide some initial feedback to patients and HCPs who make use of their system. The only role player which the MAH directly communicates with in terms of ADR reporting is the national PV centre of the country within which it is marketing its products. The MAH is legally obligated to submit all received spontaneous reports to the national PV centre, as well as to provide the national PV centre with all of the necessary documentation regarding the product which it is marketing. In the EU, according to European Medicines Agency (2010), MAHs are legally required to provide the national PV centres with a Pharmacovigilance System Master File (PSMF), a technical document which according to Article 1(28e) (European Medicines Agency, 2004) is defined as:

> "A detailed description of the pharmacovigilance system used by the marketing authorisation holder with respect to one or more authorised medicinal products."

The PSMF contains sections on the organisational structure of the MAH, the sites where PV activities take place, descriptions of the delegated PV activities, procedural documentation, and data handling and database functionality. Furthermore, MAHs can be requested at any point in time to perform post authorisation safety studies (PASS) to monitor the risk-benefit profile of their products over their entire life cycle. The findings of the PASSs are then made available to national PV centres via periodic safety update reports (PSURs) (see cell F5, in Table 4.1).

Once the ICSR has been submitted to *the* UMC's VigiBase, the information is analysed, the outputs of which are made accessible to national PV centres and MAHs around the world (see cells G5 and G6, in Table 4.1). Member countries of the PIDM pay a subscription fee for the use of *the* UMC's services, this fee is calculated using the World Bank Atlas method[1]. MAHs are also required to pay a subscription fee for the use of *the* UMC's services. The components and functionality of *the* UMC's Vigi Tools and Methods are discussed in detail in Section 4.4.

Figure 4.4 shows the communication channels used during the reporting of ADRs according to the minimum requirements for a functional national PV system as described by the WHO (World Health Organization, 2010). The minimum requirements include:

1. A **national PV centre** with designated staff (at least one full time), stable basic funding, clear mandates, well defined structures and roles, and collaboration with the WHO Programme for International Drug Monitoring.

[1]The World Bank's official estimates of the size of economies are based on GNI converted to current U.S. dollars using the World Bank Atlas method. The Atlas method smoothes exchange rate fluctuations by using a three year moving average, price-adjusted conversion factor (The World Bank, 2018).

2. The existence of a **national spontaneous reporting system** with a national Individual Case Safety Report (ICSR) form, i.e. an ADR reporting form.
3. A **national database** or system for collating and managing ADR reports.
4. A national ADR or PV **advisory committee** able to provide technical assistance on causality assessment, risk assessment, case investigation and, where necessary, crisis management including crisis communication.
5. A clear **communication strategy** for routine communication and crisis communication.

Note that no direct patient reporting is available in this context.

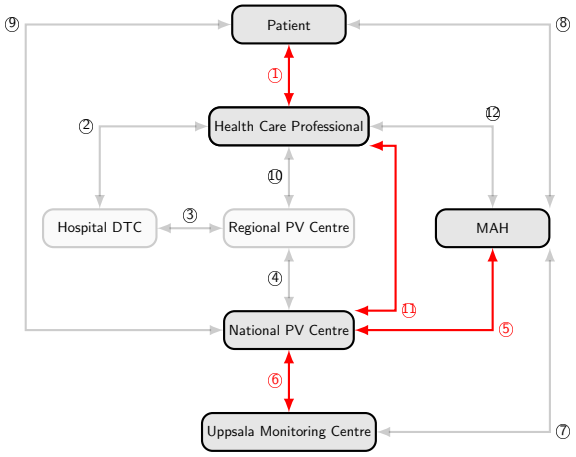

Figure 4.4: A schematic representation of the communication channels used during the reporting of ADRs in a resource limited context. Note: No patient reporting allowed.

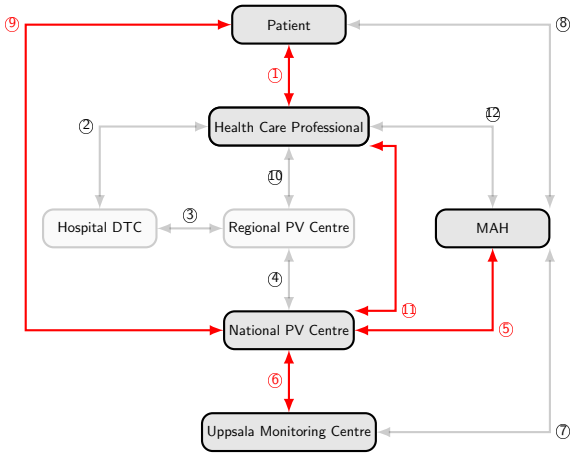

Figure 4.5: A schematic representation of the communication channels used during the reporting of ADRs in a resource limited context which allows for patient reporting.

Figure 4.5 shows the communication channels used during the reporting of ADRs in resource limited contexts, but with the addition of direct patient reporting. The short code service PRASCOR, used in Nigeria, is a good example of how the use of mobile technology can address some of the challenges relating to insufficient resources. In this instance a patient or HCP sends a free SMS message via a mobile telephone to a short code number, in this case 20543; the message must include the name of a medication and a suspected ADR. The reporter receives an automated response acknowledging receipt and providing some guidance on which steps to follow next (The Nigerian National Agency for Food and Drug Administration and Control, 2018). The national PV centre then contacts the reporter and solicits more information from them and their HCP to compile a suitably completed ICSR.

4.2 Types of reporting

The concept of ADR reporting was introduced in Chapter 3. Three methods of PV reporting were described and differentiated by the solicited or unsolicited nature of the monitoring method. In summary, Spontaneous Reporting (SR) is by definition the unsolicited reporting of ADRs, whereas the methods of Cohort Event Monitoring (CEM) and Targeted Spontaneous Reporting (TSR) involved the soliciting of ADR information from specific groups of patients. In this section the different types of monitoring methods and their objectives are discussed. Hill (2014) gives the following different objectives of PV monitoring systems:

- To establish a functional reporting system to monitor the safety of all medicines marketed within a country. This is a minimum requirement set by the WHO for a functional national PV system.
- To learn more about the benefit/risk profile of new medicines, specifically during the early post-marketing authorisation phase.
- To learn more about the ADR profile associated with a specific medicine in a given population.
- To estimate the incidence of a known ADR to a specific medicine in a given population.
- To utilise electronic health records and health registries to identify emerging drug safety concerns.

These objectives of reporting can be attributed to each of the five methods described by Tanaka (2015), shown in Figure 4.6. Moving from left to right along the Figure 4.6 it is shown that which each reporting method, the level of suspicion decreases while the amount of information increases simultaneously. The unsolicited nature of a spontaneously reported ADR implies a

certain level of suspicion in that the reporter suspects an ADR and acts upon this suspicion. On the opposite end of the spectrum there is no level of suspicion because the data already exists in the electronic health record and is available for continuous analysis. On the other hand, the level of information increases as you move across the spectrum, both in terms of quality of information and quantity of information. This will be elaborated on in the following discussion.

4.2.1 Push and pull methods in data flows

In data flow systems the notion of push and pull models is well known. Within each of these models there exists an active component and a passive component. A push model is data driven, with the sender of information actively pushing information towards the receiver. While in a pull model, the active component would be the receiver requesting the information from the sender, in this instance the receiver is in control over what information is received.

4.2.1.1 Push methods

In this section the first four reporting methods in Figure 4.6 are discussed. These four methods can be considered push PV methods in that the ADR information must be sought and accumulated before being pushed through the system towards the ICSR document that is compiled by the national PV centre.

A spontaneous reporting system involves the unsolicited, voluntary submission of ADR reports to a national PV centre and is considered a cornerstone of a national PV system according to the WHO minimum requirements as outlined in Section 4.1.2. The reporter in a spontaneous reporting system can be a healthcare professional, a pharmaceutical manufacturer, or a patient. A spontaneous reporting system allows for the reporting of all suspected ADRs and enables a national PV centre to develop a profile of ADRs that are experienced with locally used medicines.

Intensified ADR reporting can be seen as an extension to spontaneous reporting but is used specifically to learn more about the benefit/risk profile of new medicines, during the early post-marketing authorisation phase. An example of an intensified ADR reporting method is the Black Triangle Scheme used in the United Kingdom. A black triangle (▼) printed on the label of a medicinal product means that the product is being monitored more intensively. Medicines under additional monitoring could include those with new active ingredients, biological medicines, or medicines that are given conditional approval under exceptional circumstances.

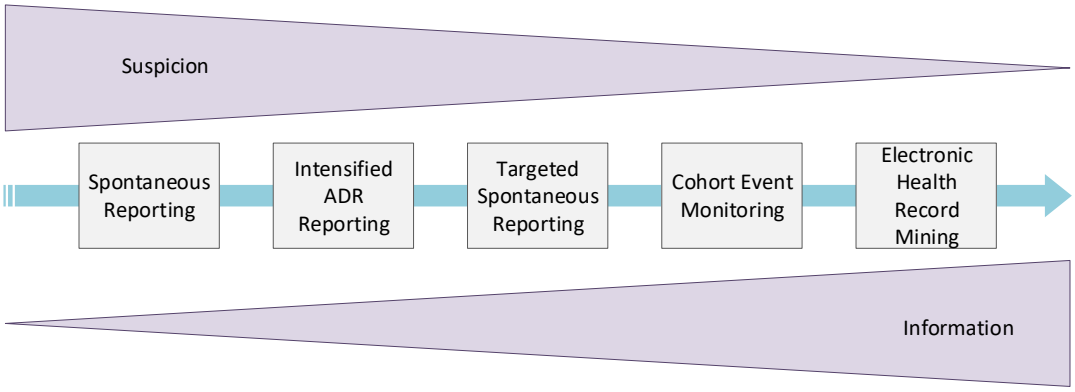

Figure 4.6: The five reporting methods and change in levels of suspicion and information (Tanaka, 2015).

Targeted Spontaneous Reporting (TSR) is a methodology which is similar to spontaneous reporting but involves well defined patient groups. TSR is an active method of surveillance in a well-defined population group whereas spontaneous reporting is a passive method of surveillance used within an undefined population (Mehta *et al.*, 2014). TSR is useful when the objective of the monitoring is to learn more about the ADR profile associated with a specific medicine in a given population, or to estimate the incidence of a known ADR to a specific medicine in a given population.

Hill (2014) defines Cohort Event Monitoring as "a prospective, longitudinal, observational, cohort study of adverse events associated with one or more monitored medicines." The primary benefit of CEM is realised when used to observe the effects of a new medicine in the early stages of post-marketing authorisation (Pal *et al.*, 2013). Although all PV monitoring methods focus on patient safety, CEM takes the approach of focussing on a specific medication for the time before and during the control period.

4.2.1.2 Pull method: Electronic health record mining

In contrast to the push methods of ADR reporting, the use of Electronic Health Records (EHRs) would result in a pull-based system. EHRs allow for the passive surveillance of drug safety concerns through the mining of information that exists within the EHR. An EHR is a single electronic document which contains a comprehensive and exhaustive record of all routinely collected, longitudinal health related data for a given patient. When information on this scale is available, the opportunity for automated data mining techniques are indisputable. EHRs can consist of aggregations of data across multiple organisations, this concept is known as record-linkage. Medical records from hospitals and HCPs, pharmacy and drug dispensary

registries, and health insurance claims could potentially contribute towards the rich data set of an EHR. Rigorous methods to systematically evaluate this data, to better understand the benefit-risk profiles of new and existing medications, are rapidly becoming a priority in the PV practices of many countries.

Currently the two largest initiatives for using EHRs as a data source for computerised data mining and signal detection are the FDA's Sentinel Initiative and the "Exploring and Understanding Adverse Drug Reactions by integrative mining of clinical records and biomedical knowledge" (EU-ADR) initiative (Patadia *et al.*, 2015). The EMA's EU-ADR project uses eight European population-based administrative and healthcare databases from the UK, Netherlands, Germany, Italy, and Denmark (Pacurariu *et al.*, 2015). The data in the EU-ADR project is representative of approximately 20 million patients, with drug exposure data sourced from prescription and dispensing data according to the Anatomical Therapeutic Chemical (ATC) Classification System. The ATC system classifies pharmaceutical products in a hierarchy with five levels, an example of the ATC classification for metformin, the most frequently prescribed drug for the treatment of type 2 diabetes, is shown in Table 4.2. Prescriptions with the same ATC codes can be grouped together and prescription start dates and end dates are used to determine concomitant drug use.

Table 4.2: ATC classification for metformin. (WHO Collaborating Centre for Drug Statistics Methodology, 2018)

A	Alimentary tract and metabolism (1st level, anatomical main group)
A10	Drugs used in diabetes (2nd level, therapeutic subgroup)
A10B	Blood glucose lowering drugs, excl. insulins (3rd level, pharmacological subgroup)
A10BA	Biguanides (4th level, chemical subgroup)
A10BA02	metformin (5th level, chemical substance)

The primary limitation of EHR mining is that the data in EHRs is not collected for the purpose of PV activities such as signal detection. For this reason attention must be given to finding the appropriate signal detection methods that can be applied to EHRs so as to 'find the needle in the haystack' as it were.

4.3 The Individual Case Safety Report

Once the spontaneous reporting process has been initiated, as discussed in Section 4.1.2, the national PV centre compiles a standardised electronic document known as an Individual Case Safety Report (ICSR). The ICSR can be updated to include all information referring to a specific ADR generated by the patient and HCP alike. The ICSR is a primary source of data in PV. Due to various international and national laws and regulations, the information within ICSRs needs to be transmitted (International Council for Harmonisation, 2001):

- from identifiable reporters to RAs, national PV centres, and MAHs,
- between RAs,
- between MAHs and the RAs of the jurisdictions within which they operate,
- within RAs or MAHs, and
- from national PV centres to the WHO Collaborating Centre for International Drug Monitoring, *the* UMC.

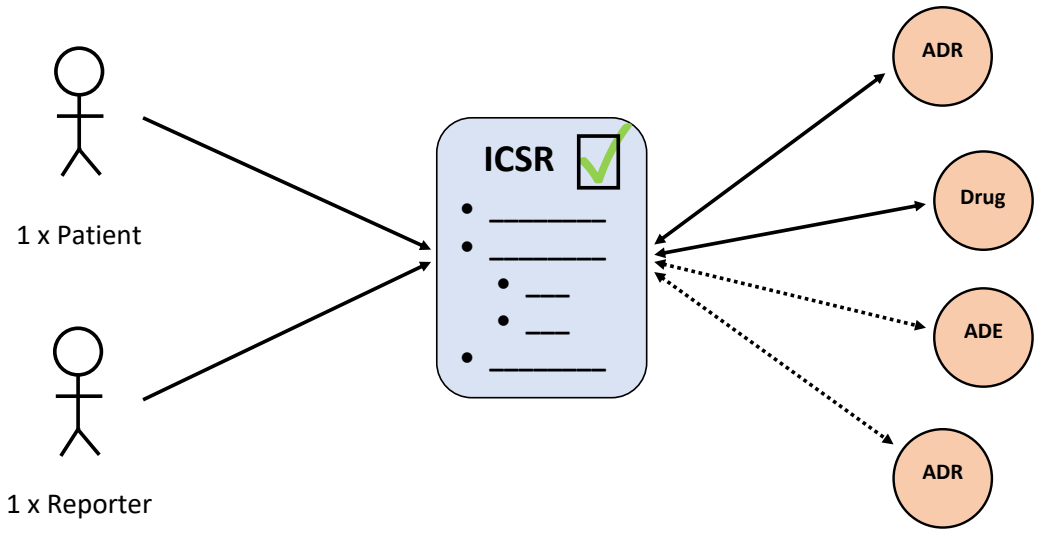

Figure 4.7: Minimum requirements for a valid ICSR per *the* UMC guidelines.

The minimum required information for a valid ICSR is shown in Figure 4.7. According to *the* UMC and the ICH E2B standard, the minimum required information for a valid ICSR is:

1. One identifiable patient[1],
2. One identifiable reporter,
3. One reaction/event, and
4. One suspected drug.

The minimun administrative information that is needed to correctly identify and process a report in *the* UMC's VigiBase is:

1. Sender's unique case identification number,
2. Worldwide unique case identification number,
3. Sender identifier, and
4. Date of receipt of most recent information.

The personal information of the patient and the reporter must under no circumstances be sent to VigiBase as this information is confidential.

4.3.1 The new ICH E2B(R3) standard

Successful electronic transmission of information relies on the definition of standard data elements. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) published a guideline "Data Elements for Transmission of Individual Case Safety Reports" in 1997. The guideline was proposed to address challenges faced by the large number of participants in a world-wide exchange of information. The ICH sought to bring together regulatory authorities and the pharmaceutical industry to harmonise scientific and technical aspects of pharmaceutical regulation. In 2005 the implementation of the electronic submission of ICSRs (ICH E2B(R2)) became wipespread in the ICH regions, being Japan, the European Economic Area, and the United States of America. ICH E2B(R3) was initiated in 2006 when the ICH Steering Committee took the decision to collaborate with multiple international Standards Development Organisations (SDOs) in an effort to achieve greater interoperability across the global health and regulatory systems. The project was named the Joint Initiative on SDO Global Health Informatics Standardization and involved, among others, the International Organisation for Standards (ISO), Health Level 7 (HL7), and the European Committee for Standardization (CEN)(European Medicines Agency, 2016b).

[1]There exist several data elements which can be considered sufficient to define an identifiable patient or reporter, these include initials, age, sex, address, qualifications etc. Additional rules for the required 'minimal information' might be enforced at the regional PV centre level.

By 2011 multiple additional SDOs had joined the joint initiative, including the Clinical Data Interchange Standards Consortium (CDISC), the International Health Terminology Standards Development Organisation (IHTSDO), and Global Standards One (GS1). The new ICH E2B(R3) standard was published in 2011 (ISO/HL7 27953-2:2011 , HL7).

An ICSR that is in compliance with the ICH E2B(R3) standard is developed using *eXtensible Markup Language* (XML) encoding syntax, a programming language that is both human-readable and machine-readable. RAs are advised to enforce the use of the ICH E2B(R3) format for electronically capturing and transmitting ICSRs by MAHs. According to European Medicines Agency (2016b) and the FDA Centre for Drug Evaluation and Research (2014) the ICH E2B(R3) format for electronically capturing and transmitting ICSRs is currently in use in Japan, the European Union, and the United States of America. The benefits of the new ICSR standard include a general improvement of the ICSR format due to almost 10 years of operational experience, additional data elements which increases the quality of the ICSR, alignment with the ISO Identification of Medicinal Products (IDMP) standards, improved interoperability with global health and regulatory systems, as well as improved harmonisation of data formats in use beyond the ICH region.

4.3.2 The structure of an ICSR

Figure 4.8 is a relational diagram showing the components of an ICSR. The ICSR is made up of two primary sections, section A on the left hand side depicted in yellow is concerned with administrative and identification information. Section B on the right hand side, contains information on the case. The code sets, terminologies and vocabularies used to populate an ICSR can be found in the Medical Dictionary for Regulatory Activities (MeDRA) and the WHODrug Dictionary.

Compatibility between the ICH E2B(R2) and the new ICH E2B(R3) formats must be ensured, for both forward compatibility and backward compatibility. Compatibility means that different PV systems which interact on the basis of either ICH E2B(R2) or ICH E2B(R3) can support the electronic exchange of PV data.

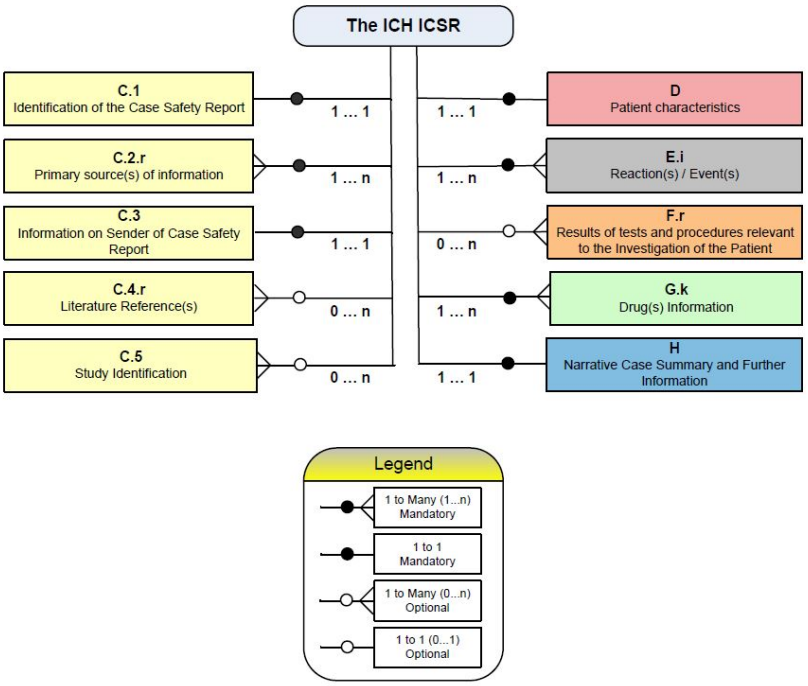

Figure 4.8: The ICH E2B(R3) ICSR structure. (ISO/HL7 27953-2:2011 , HL7)

4.4 WHO solution: the Uppsala Monitoring Centre and their software tools and methods

The UMC has developed a set of software tools and methods for the communication of PV data. The software tools and methods which facilitate the management of PV data, are collectively referred to as the "Vigi tools and methods"[1]. The tools include VigiBase, VigiLyze, VigiAccess, and VigiFlow; while the methods include vigiGrade, vigiMatch, vigiPoint, vigiTrace, and vigiRank (*the* Uppsala Monitoring Centre, 2018b). A brief description of each of these tools and methods is provided below:

- **VigiBase**: *The* UMC's global ICSR database. Developed in 1968, VigiBase is the largest database of its kind in the world, with over 20 million reports of suspected ADRs of medical products (*the* Uppsala Monitoring Centre, 2018f). Data in VigiBase is encoded according to certain terminology code sets, such as MedDRA and WHODrug, the original terminology used for coding ADRs was WHO-ART, until it was replaced by MedDRA in 2008. The hierarchical structure of the MedDRA code set can be seen in Figure 4.9. VigiBase accepts ICSR data from over 110 member countries of the WHO Programme, representing over 90% of the world's population. According to the 2016 UMC Annual

[1]The vigi methods (vigiRank, vigiMatch, vigiGrade, vigiPoint, and vigiTrace) are stylised by *the* UMC, with a lower-case 'v', while the vigi tools are stylised with an upper-case 'v'.

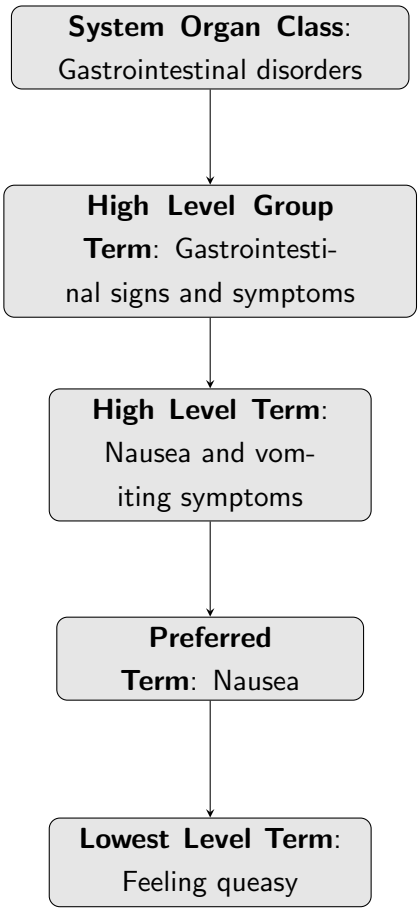

Figure 4.9: The five levels to the MedDRA hierarchy. (MedDRA, 2018).

Report, 11.5% of the ICSRs in VigiBase come from low- and middle-income countries (*the* Uppsala Monitoring Centre, 2016).

- **VigiSearch**: A powerful search tool which can be used to find individual case safety reports (ICSRs) collected in VigiBase from all participating countries. Replaced by VigiLyze in July 2013.

- **VigiMine**: A statistical tool within VigiSearch with vast statistical material calculated for all Drug-ADR pairs available in VigiBase. The main features include the disproportionality measure (IC value) stratified in different ways and useful filter capabilities. Replaced by VigiLyze in July 2013.

- **VigiLyze**: A web-based resource that provides a quick and clear overview of VigiBase data in tabular and graphical formats. VigiLyze takes advantage of the well structured nature of the data within VigiBase to provide search and analysis functions. Due to the well-known problem of under-reporting, free access to VigiLyze is given to all national PV centres, the aim of this is to allow countries with low numbers of ICSRs to complement their data with the global database.

- **VigiAccess**: Online resource for the general public to gain access to VigiBase data. VigiAccess searches the VigiBase database for ADR data relating to a pharmaceutical product that the user has specified in the VigiAccess search. The user provides the tradename of the drug as it would appear on the product packaging. The search returns the name of the product together with the active ingredient of the product. The total number of records retrieved is shown together with the distribution of the reports in terms of: ADRs, geographical distribution, age group distribution, patient sex distribution, and ADR reports per year. The summary statistics that VigiAccess provides are formatted in a way that protects patient confidentiality and individual country data.

- **VigiFlow**: A web-based ICSR management system. VigiFlow is available for use by national PV centres of countries belonging to the WHO Programme for International Drug Monitoring, *the* UMC does however charge a license fee for the use of VigiFlow, this fee is determined by the World Bank Atlas method. As of October 2017 there are over 70 countries which make use of VigiFlow (*the* Uppsala Monitoring Centre, 2017). Through its compliance with the new ICH E2B(R3) standard, VigiFlow supports the collection, processing and sharing of ICSRs to facilitate effective data analysis. Data transmitted via VigiFlow is structured with WHODrug and MedDRA codes to ensure compatibility. VigiFlow ensures that ICSR data can be imported and exported in a harmonised format through the use of XML-files, these files can be easily exchanged with

external stakeholders such as national PV centres and pharmaceutical companies, while being stored in VigiBase. Due to the web-based nature of VigiFlow all that is required for its effective use is a suitable computer and internet access, thus eliminating the need for local installations, back-ups or maintenance. Unfortunately VigiFlow provides no off-line functionality. VigiFlow encrypts the data and ensures that the information is only accessible by authorised parties. Although VigiFlow is strongly recommended to national PV centres as a means of submitting ICSRs to VigiBase, it is not mandatory for reporting to VigiBase. According to the 2015 Annual Report by *the* UMC, 74 national PV centres make use of VigiFlow as their ICSR management system, with a total of 480 485 ICSRs having been submitted to VigiBase from the VigiFlow system (*the* Uppsala Monitoring Centre, 2016). In October 2017 a new version of VigiFlow was released (*the* Uppsala Monitoring Centre, 2017). The update supports the recording of causality assessment results, and now includes options for WHO-UMC causality, WHO AEFI (Adverse event following immunization) causality, and Naranjo methods[1]. As of October 2017 the default medical terminology in use is MedDRA, those countries which still use WHO-ART (WHO Adverse Reaction Terminology) will be assisted by *the* UMC to convert their data to be MedDRA compliant.

- **vigiRank**: Predictive model that ranks PV safety signals according to multiple aspects of strength of evidence. vigiRank was implemented in *the* UMC signal detection process in 2014 (*the* Uppsala Monitoring Centre, 2018d).

- **vigiMatch**: Probabilistic record-matching method to detect unexpectedly similar pairs of records in a database. The vigiMatch algorithm was included in the VigiLyze tool in November of 2017 (*the* Uppsala Monitoring Centre, 2018a). The algorithm calculates a match score for a pair of ICSRs, if the match score exceeds a certain threshold then the ICSRs are flagged as suspected duplicates. If suspected duplicates of ICSRs exist, then only the ICSR with the highest vigiGrade completeness score is included in calculations.

- **vigiGrade**: Multidimensional measure of data quality in PV (completeness, relevance, consistency, etc.). vigiGrade assigns each ICSR with a completeness score, this is achieved by selecting critical data entry fields and giving them a score; these individual scores can then be weighted and combined to produce a total score for the ISCR, the maximum score is 1.0 (*the* Uppsala Monitoring Centre, 2018d).

[1]The Naranjo Algorithm, or Adverse Drug Reaction Probability Scale, is a method by which to assess whether there is a causal relationship between an identified untoward clinical event and a drug using a simple questionnaire to assign probability scores (Naranjo *et al.*, 1981).

- **vigiPoint**: An algorithm to pinpoint the key features of a subset of database records in contrast to a broader set. These features include, but are not limited to age, sex, co-reported drugs, and adverse reactions.
- **vigiTrace**: Suite of analytics methods for the analysis of longitudinal event history data, including chronographs for statistical graphical overviews and the calibrated self-controlled cohort design for temporal screening.

Some of the tools from the software environment are depicted in Figure 4.10.

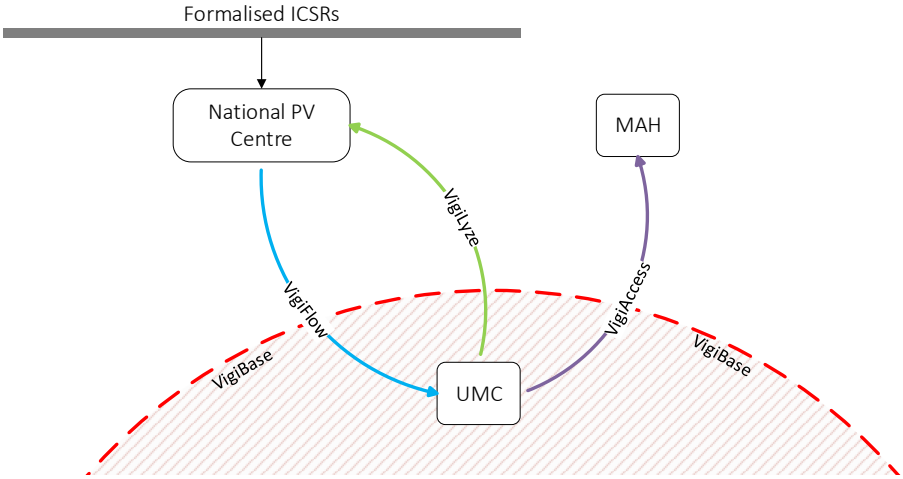

Figure 4.10: The flow of information pertaining to ICSRs through the use of *the* UMC's software environment.

Figure 4.10 shows how the national PV centres of participatory countries submit ICSRs via VigiFlow to *the* UMCs VigiBase, these national PV centres can also explore VigiBase data through the VigiLyze interface. Marketing authorisation holders can access the data within VigiBase by making use of the VigiAccess interface. MAHs are subjected to varying laws and regulations around the world, and it is for this reason that they are obligated to submit any PV data they receive to the national PV centre of the country within which they are marketing their pharmaceutical products.

4.5 Case studies: What is the current situation?

According to the 2016 annual report by *the* UMC, by June 2016 the total number of ICSRs received into the VigiBase database was 13 208 000, representing an increase of 18% from the previous year (*the* Uppsala Monitoring Centre, 2016). 11.5% of the ICSRs in VigiBase were received from low- and middle-income countries (LMICs), an increase of 32% from 2015.

Figure 4.11 shows the country distribution for ICSRs received by VigiBase during 2016. Currently 75% of the PIDM countries adhere to ICH E2B standard, most will be focussing their efforts on transitioning from the ICH E2B(R2) to the new ICH E2B(R3) standard.

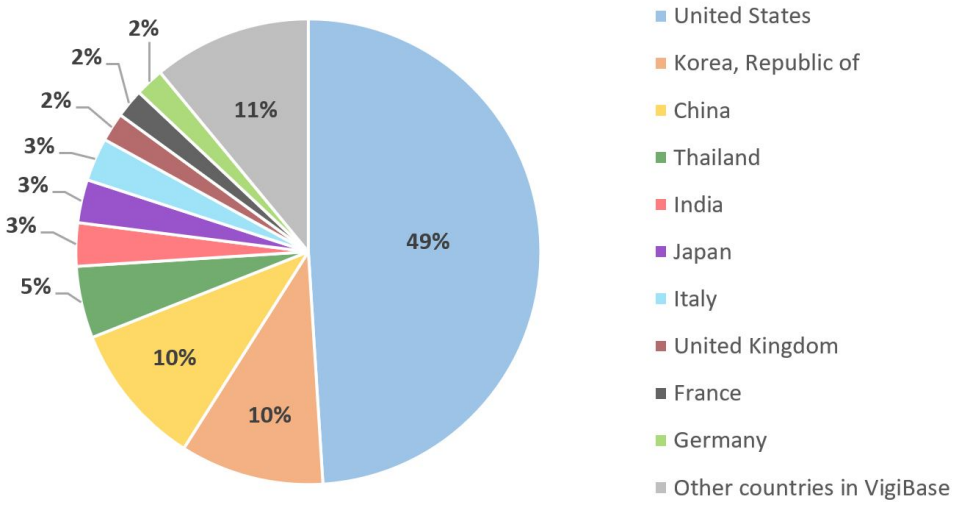

Figure 4.11: Country distribution for ICSRs received by VigiBase during 2016 (*the* Uppsala Monitoring Centre, 2016).

While Figure 4.12 shows countries distributed according to time elapsed since last submission of ICSRs to VigiBase, as of June 2016.

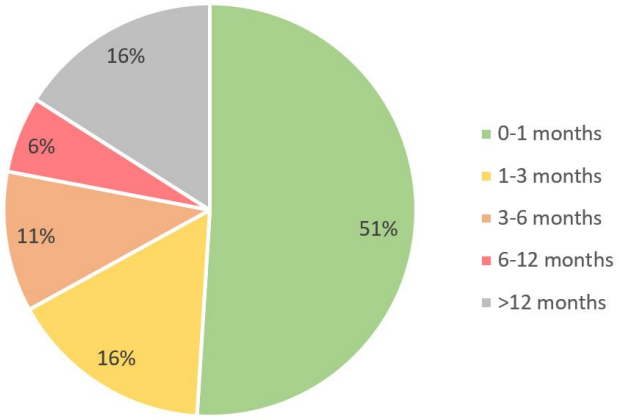

Figure 4.12: Countries distributed according to time elapsed since last submission of ICSRs to VigiBase, as of June 2016 (*the* Uppsala Monitoring Centre, 2016).

4.5.1 High income countries: Pharmacovigilance in the European Union and the United Kingdom

The EU pharmacovigilance system is supported by a regulatory network consisting of National Competent Authorities (NCAs), the EMA, the European Commission (EC) and a set of legal

frameworks. The legislation found in the European Medicines Agency (2010) aims to strike a balance between two objectives, namely the free movement of pharmaceutical products in the EEA, and the simultaneous protection of public health throughout the EU. There are two mechanisms by which pharmaceutical companies can obtain marketing authorisation, the first being through a decentralised process involving individual Member States, or by a centralised process involving the EMA. If a product is centrally authorised it is referred to as a Centrally Authorised Product (CAP) and may be marketed anywhere within the EU, similarly if a product obtains authorisation from a Member State NCA then the product is referred to as a Nationally Authorised Product (NAP)(Santoro *et al.*, 2017). During pre-marketing drug development, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) assesses the risks and benefits of all products seeking marketing authorisation to determine their quality, safety, and efficacy. The Co-ordination Group for Mutual Recognition and Decentralised procedures - Human (CMDh) is the chief decision-making body when pharmaceutical products are marketed in the EU through the decentralised process.

In the EEA, patients and HCPs can submit reports of suspected ADRs to their respective NCAs or the MAH of the drug in question. The reports are then submitted to EudraVigilance, a centralised database of ADR reports in the EU which is maintained by the EMA. Transparency is a priority in the EU PV system and as such the general public can access annonymised data from EudraVigilance through a website. The number of ICSRs submitted spontaneously for CAPs can also be seen by the general public. The EudraVigilance system is compliant with the ICH E2B(R2) standard, as is currently being enhanced to comply with the new ICH E2B(R3) standard for ICSRs. The EMA also requires all MAHs to submit information on all their authorised medicines, as well as the PV system master file, which must be compliant with standards for the identification of medicinal products. NCAs are responsible for the collection of all reported ADRs, and must appoint at least one qualified person for pharmacovigilance (QPPV).

We now consider ADR reporting in the United Kingdom. PV in the UK is conducted by the Medicines and Healthcare products Regulatory Agency (MRHA). The UK established its PV system with the introduction of the Yellow Card Scheme in 1964. In the 1960's ADR reporting via the Yellow Card Scheme was restricted to physicians and dentists only, with other HCPs being allowed to report since the 1990's, and direct patient reporting being introduced in 2005. This meant that patient reporting in the UK was permissible 5 years prior to the European Medicines Agency (2010) which introduced patient reporting throughout the EU. While MAHs are legally obligated to report all reports of suspected ADRs to the MHRA database, HCPs are not legally but professionally obligated to report ADRs and serious ADRs, with encouragement to report all suspected ADRs associated with medicines on the Black Triangle Scheme (▼) list.

In 2005, the MHRA launched the "Yellow Card App" for smartphones, an additional reporting method for patients to make use of, along with telephone reporting and paper-based reporting via the mail. In 2015, the MHRA received 40 000 ADR reports, an increase on previous years which it attributes to the improved patient reporting channels and general promotion and awareness of ADR reporting conducted by decentralised MRHA sites throughout the country (Kaeding *et al.*, 2017). The MHRA must submit all serious ADR cases to the EMA within 15 days of receiving them.

4.5.2 Middle income countries: Pharmacovigilance in South Africa

South Africa is faced with the large burden that is one of the highest co-morbidity rates of HIV and TB infections in the world. The high prevalence of infectious diseases, together the use of medicines and therapies of ever-increasing complexity, necessitates a strong pharmacovigilance system to reduce morbidity, mortality and the associated costs (Terblanche *et al.*, 2017).

PV activities in South Africa are coordinated by the Medical Controls Council (MCC), under the Medicines and Related Substances Control Act of 1965[1]. South Africa was the first African country to become a full member of the WHO PIDM having joined in 1992 and established the National Adverse Drug Event Monitoring Center (NADEMC) in 1987 through collaboration with the University of Cape Town. The MCC also established a WHO collaborating centre in 1995 for regional training in drug policy in the School of Pharmacy at the University of the Western Cape. Although legal provisions for PV activities are available, there is no national PV policy in South Africa (Mehta *et al.*, 2014). NADEMC was instrumental in setting up the adverse events following immunization (AEFI) targeted spontaneous reporting (TSR) system for the expanded programme for immunization (EPI) in 1998. In 2003 provincial TSR systems were established for the monitoring of ADRs associated with the roll-out of the national antiretroviral (ARV) treatment program (Mehta *et al.*, 2017).

South Africa is currently undergoing a transition process in that the MCC is being replaced by the South African Health Products Regulatory Authority (SAHPRA). With this transition it is envisioned that a strengthening of PV activities and legislation will be achieved. Currently, the reporting of suspected ADRs to the NADEMC by industry and HCPs is voluntary but the regulations in the Medicines and Related Substances Control Amendment Act require MAHs to report all received reports of ADRs within 15 days of initial receipt. This reporting is performed via telephone, facsimile, or regular mail. Direct patient reporting is not currently supported in South Africa and in the event of a patient reporting to a MAH, the MAH is obliged to encourage the patient to consult with their HCP and complete the reporting process with their

[1] Medicines and Related Substances Control Act 101 of 1965 after amendment by the Medicines and Related Substances Control Amendment Act (Act 90 of 1997)

assistance. The current ADR form in use in South Africa is not ICH E2B(R3) compliant, however it is worth noting that with the current change in PV stewardship (the introduction of SAHPRA), this could change in the near future. Representatives from the MCC were invited to Osaka Japan in November 2016 to observe the assembly of several members of the ICH with regards to discussions surrounding the implementation guideline for the new ICH E2B(R3) standard for ICSRs (The International Council for Harmonisation, 2016). Up to 2015, South Africa had contributed 28 609 case report forms to the WHO PIDM database. Under-reporting of ADRs and the multiple contributing factors to under-reporting were discussed in Chapter 3. Substantial evidence of internationally widespread under-reporting is present in the literature. A South African study performed by Terblanche *et al.* (2017) showed that awareness of ADR reporting among HCPs in a South African district hospital was only 18.9%, however 96.2% agreed that ADR reporting was necessary with 89.4% indicating that ADR reporting is their professional obligation. The study found that only 12.1% of HCPs in the district hospital had ever reported an ADR. To improve HCP's knowledge, attitudes and perspectives on ADR reporting, and thereby strengthen spontaneous reporting; appropriate education and training of HCPs is crucial.

According to the Strengthening Pharmaceutical Systems (SPS) Program (2011) assessment of PV systems in sub-Saharan Africa (SSA), South Africa has the strongest pharmaceutical industry, accounting for 70% of the the pharmaceutical market, in SSA. The report concludes that although encouraging trends are seen in the South African pharmaceutical industry with development in terms of structure, staff and SOPs, there remain considerable challenges in ADR reporting, data collation, risk evaluation and decision-making. The report highlights the low level of awareness on reporting regulations, guidelines and ADR forms. The current PV strategy in SA seeks to augment passive surveillance systems such as spontaneous reporting of ADRs, with active surveillance approaches. The primary drawback of spontaneous reporting systems is their inability to quantify ADR incidence or to identify risk factors, for this reason, the MCC has chosen to take a mixed approach to PV in SA (Mehta *et al.*, 2017).

4.5.3 Low income countries: Pharmacovigilance in Burkina Faso

According to *the* UMC, Burkina Faso first established its PV system in 2005 (*the* Uppsala Monitoring Centre, 2011). Subsequently, in 2010 Burkina Faso became an official member of the WHO PIDM. An event which contributed significantly to the development of PV activities in Burkina Faso was the roll-out of the meningococcal A conjugate vaccine *MenAfriVac*™ in 2010 (Ouandaogo *et al.*, 2012). Before 2008 PV activities were limited to mass vaccination campaigns. However, in 2008 under supervision from WHO representatives, PV protocol was

established within the Ministry of Health, the "Direction Gnrale de la Pharmacie, du mdicament et des laboratoires, Sant, Mdicament BF, Laboratoire" (DGPML), in preparation for the roll-out of *MenAfriVac™*. The objectives of the protocol included the detection and identification of all serious AEFIs, thereby enabling the appropriate action to be taken and corrective measures to be put in place (Compaore, 2010). The protocol was presented to the WHO Global Advisory Committee on Vaccine Safety (GACVS) in Geneva in 2009. The surveillance of the *MenAfriVac™* roll-out was performed through two systems, a targeted spontaneous reporting system, with the intention to find potentially serious AEFIs; as well as a passive spontaneous reporting system for the identification of any potential AEFIs. Burkina Faso benefited greatly from this Vaccination Programme as it allowed for the NRA to develop capacity and the relevant functionality to manage PV activities in other public health programmes.

A study by Kabore *et al.* (2013) conducted an analysis of the PV system in Burkina Faso with the use of the USAID Indicator-based PV Assessment Tool (IPAT). The study found that the two areas which scored the least were the 'policy, law, and regulation' and the 'signal generation and data management' categories. The PV system in Burkina Faso failed to meet the requirements of 7 out of a total of 22 core indicators. The 7 indicators which were not met are:

1. Specific references to PV in the national medicines legislation.
2. Availability of a Question-Answer service on the safety of medicines.
3. Existence of national PV guidelines.
4. Existence of patients' safety standard operating procedures.
5. Existence of a platform of coordination across all PV stakeholders.
6. Existence of a form for reporting suspected defective product quality.
7. Existence of a form for reporting suspected treatment failure.

Additionally, 3 of the 5 largest hospitals in Burkina Faso failed to meet two indicators: the existence of a PV unit or DTC, and the existence of a bulletin on the safety of medicines. Encouraging findings from the assessment included membership of *the* UMC, allowing the use of the ICH E2B compliant ICSR form through the web-based portal VigiFlow. Kabore *et al.* (2013) found that at the time of their study, VigiBase has received 1986 suspected ADR reports from Burkina Faso, this is largely attributed to the targeted spontaneous reporting initiative for the *MenAfriVac™* vaccination programme.

According to the minimum requirements for a functional national PV system as described by the WHO (World Health Organization, 2010), Burkina Faso's' PV system is considered non-functional as it does not meet the 22 core indicators of a functional PV system. Due to the low ratio of physicians and pharmacists to patients in 2012, 1:21 320 and 1:82 656 respectively (Burkina Faso Ministre de la Sant, 2012), it is clearly a necessity to ensure that ADR reporting in Burkina Faso can be achieved in a streamlined and timely manner, so as to not increase the already heavy workload of HCPs. The formation of hospital DTCs should have a positive influence on ADR reporting rates, with little to no extra resources required as the constituent members of a DTC are all present within a hospital in any event.

4.5.4 Key differences between the three presented cases

The strength of the EU's PV system lies not only in the availability of resources but in the extensive and exemplary set of laws and regulations set out by the EC and EMA. PV systems in LMICs are typically not predicated on solid legal and regulatory foundations, as well as being mostly under-funded and suffering from a lack of suitably trained professional staff.

If LMICs are to bridge the gap between their current situation and achieving the functionality of a PV system such as the EU PV system, technological innovations must be embraced wherever possible. Nigerias' PRASCOR system is a good example of how to increase patient involvement and alleviate the workload of HCPs.

Collaboration between NCAs and with organisations such as the WHO PIDM should be encouraged so as to maintain adherence to current best practices and improved SOPs. To facilitate this exchange of information, a concerted effort must be made by NCAs to comply with the ICH E2B(R3) standard.

4.6 Resource availability and resource efficiency

Developing countries, the LMICs, have the highest disease burdens and are therefore the largest consumers of critical medicines, particularly vaccines. Yet, in 2016 only 11.5% of the ICSRs in VigiBase were received from LMICs. One of the largest challenges facing the global PV landscape is the matter of resource availability and resource efficiency. It is undeniable that the most disadvantaged countries, the LMICs, are those which stand to benefit the most from global PV initiatives. It is therefore the socially just and moral imperative that the international community provides the necessary resources required to have a functional global PV network. The development of strong drug safety legislation in the EU, in particular the European Medicines Agency (2010), has led to significant improvements in coordination and data collection. This legislation also allows for the EMA to charge fees to pharmaceutical

companies which market their products in the European Economic Area (EEA); the proceeds from which are used to strengthen PV systems.

4.7 Towards interoperability

After considering differences and similarities in the way in which high income-, middle income-, and low income-countries conduct PV it is clear that finding a solution to the global harmonisation of PV is not as straightforward as employing standardised technologies. The discussion must take into consideration a number of other factors, including the different goals and perspectives of the multiple different stakeholders conducting PV, as well as understanding and categorising challenges and obstacles to harmonisation in terms of organisational, behavioural, operational, technical, and economic factors. These goals and perspectives are discussed in more detail in Chapter 7.

After considering the challenges in PV as described in Chapter 3 and understanding how PV systems function in terms of generating data, capturing data, and presenting data (discussed here in Chapter 4 and seen in Figure 4.13) it becomes clear that the majority of the challenges faced in PV are found in the activities leading up to the creation of the ICSR document.

For these reasons it is clear that there is considerable value in the potential creation of a Capability Maturity Model-like tool (CMM) with a behavioural science focal point, to assist with conceptualizing intervention and interaction strategies so as to achieve interoperability across multiple systems. This CMM-like tool could be used by governments or any entity wishing to conduct PV activities to measure and assess their PV capabilities so as to guide them towards reaching ICH E2B(R3) compliance. Thus, contributing maximally to PV on a global scale, while also receiving maximum value from the services offered by *the* UMC.

4.7.1 Targeting the ICSR: A common goal

As shown in Section 4.3 the electronic submission of ICSRs is outlined by the newly developed ICH E2B(R3) message standard. The standard was developed for the expedited exchange of

Figure 4.13: The flow of data in PV reporting.

safety information between systems subjected to various national and international rules and regulations. The exchange of patient safety information has been extensively covered in this chapter. As the ever increasing demand for world-wide data exchange continues, there has been a shift from paper-based systems to the electronic transmission of ICSRs using the ICH E2B(R3) standard.

Adding to the complexities already faced in the PV landscape, patient safety messages must be transmitted throughout the product life-cycle. It is clear that harmonisation is of vital importance when it comes to avoiding difficulties in reconciling ICSRs on a global level, which the World Health Organisation seeks to achieve. The ICSR described in Section 4.3 is the culmination of efforts to standardise reporting in PV. The recently developed ICSR standard, the ICH E2B(R3) is a testament that standardised solutions do exist in practice but the challenge standing in the way of worldwide system interoperability lies not in developing these standards, but rather in the adoption and implementation of these standards.

4.7.2 Differing goals and perspectives in PV and strategic alignment

The different goals of the three primary role players (*the* UMC, MAHs and RAs) who conduct PV activities and stand to gain value from this research were outlined in Section 1.2. Due to these differing goals and perspectives, it is important to create a tool which can be of value to each of these role players, as we know that the cooperation and interaction between these role players is critical to the overall success of the global PV system.

4.7.3 A maturity model approach to guide organisations to interoperability and ICH E2B(R3) compliance

Given the barriers to the adoption and implementation of the ICH E2B(R3) standard, as well as the different goals and perspectives of the major PV role players, a solution must be developed which caters to the different needs and priorities of the end-users. Maturity models are valuable in helping organisations understand their current position and capabilities, as well as offering guidance through strategically linked continuous improvement processes. In short, maturity models are tools birthed from the field of total quality management and help organisations transition from an 'As-is' state to a 'To-be' state. A maturity model will result in the identification of the relevant domains and sub-domains for PV system interoperability as well as enable each of the various PV role players to measure the maturity of the various components of their PV systems, offering guidance on which actions to take in order to reach a greater level of maturity. Further discussion relating to maturity models and interoperability can be found in Chapter 5.

4.8 Chapter 3: Conclusion

This chapter described the key role players in the global PV system, as well as the communication channels between the key role players and the flow of information through the PV system. The different methods for reporting ADRs were discussed and the current best practices were described. A comparison between methods currently in use by three selected countries was made and their respective differences and discrepancies were discussed. A new approach to addressing the challenges of under-reporting was introduced. The concept of maturity models was introduced as a means of addressing the challenges facing ADR reporting within the PV context and the value of taking a sociotechnical systems perspective during the development of a maturity model was also briefly introduced.

Chapter 5

Maturity models and interoperability

In this chapter the concept of a maturity model (MM) is explored and defined within the context of this study. The history of MMs as well as their various types and purposes is explored. The concept of interoperability is also discussed, with a particular focus on the interoperability of health information technologies (HITs) in the eHealth field. The chapter concludes with a discussion on the need to take a sociotechnical approach to introducing MMs within an eHealth context.

5.1 Background

In recent years, through the combination of an ever increasingly competitive environment, innovation, and the rate of change in technology, there has been an increase in the introduction of new systems, business processes, markets, and enterprise integration approaches. As this trend increases, many enterprises and organisations are faced with the complex task of keeping up to date. Information and operational technologies are exhibiting ever shortening life-cycles and disruptive innovation is continually putting pressure on enterprises and organisations to adapt to change or suffer the consequences.

Along with these changes, it is important for an organisation to be able to manage the interaction of their systems and processes, as well as to be able to monitor progress and measure how well they are adapting to these changes. Equally important for an enterprise or organisation is to have an understanding of the effects of poor interaction between systems and processes which could ultimately impact interoperability, safety, reliability, efficiency, and effectiveness.

Maturity models have been proposed as a solution to many of these problems. A maturity model is a tool which can assist organisations in tackling problems and challenges in a logical, structured manner. Maturity models in their most basic form, provide an organisation with a benchmark against which their capabilities can be measured, as well as providing a roadmap to guide improvement initiatives when moving forward.

5.1.1 Early maturity models

Maturity models as we know them today owe their origin to the fast growing body of knowledge which was first applied by Nolan (1973) of Harvard University in 1973. The model he published was a staged maturity model for growth in IT organisations. The development of the Capability Maturity Model® (CMM) followed, in the 1980's, by the Software Engineering Institute (SEI) at Carnegie Mellon University in Pittsburgh, Pennsylvania. The CMM was requested by the US Department of Defence and included organisational best practices for software development (Pöppelbuß & Röglinger, 2011).

The five maturity levels that are associated with the business areas and processes of the CMM were introduced in 1991 as a continuation of the work done in the 1980's. It was after the introduction of these five maturity levels that the principles and concepts of process maturity began to be applied more generically, to non-software processes (Caralli *et al.*, 2012). In 2002 the SEI published an update to the CMM framework, the CMMI® (Capability Maturity Model Integration), to integrate and standardise the separate models of the CMM. In 2018, the CMMI Institute released the CMMI® Developement V2.0 which was "designed to meet the challenges of the changing global business landscape, and drive business performance through building and benchmarking key capabilities" (CMMI Institute, 2018).

5.2 Maturity models

A maturity model is typically made up of a set of characteristics, indicators, attributes, or patterns[1] that represent progression and achievement in a particular domain or discipline (Caralli *et al.*, 2012). Maturity models allow organisations to evaluate their practices and processes against an established benchmark. In doing so, organisations are able to measure their 'as-is' capability and then make use of the model to drive improvement and control progress (Röglinger *et al.*, 2012).

Maturity models typically comprise various maturity levels, usually three to six. A maturity level is a set of distinguishable attributes which relate to their respective level and domain. A domain could be a business process, system component, or an organisation; the maturity level of the domain is identified where the attributes described most accurately represent the current state of the domain.

Caralli *et al.* (2012) state that for a MM to be considered effective and impactful, the 'measurable transitions' between levels should be based on empirical data that has been validated in practice. Each level in the model must be validated as being more 'mature' than the previous

[1] Characteristics, indicators, attributes, or patterns are hereafter referred to collectively as *attributes*.

level, against best practices. In other words, that which constitutes 'maturity' must be well characterised and validated.

Caralli *et al.* (2012) also state that an effective MM must provide the following uses:

- a place to start;
- the benefit of a community's experience and knowledge;
- a common language and a shared vision;
- a way to define what improvement and 'maturity' means for an organisation;
- a framework for prioritising actions; and
- a roadmap for return on investment (ROI) for increased maturity.

Some authors have criticised MMs for oversimplifying reality and have stated that MMs too often lack empirical foundation (De Bruin *et al.*, 2005). Furthermore, Pöppelbuß & Röglinger (2011) pose that MMs have the tendency to neglect the potential existence of multiple equally advantageous paths to maturity. King & Kraemer (1984) warned those developing MMs to not focus solely on a sequence of levels toward a predefined 'end state', but rather to focus on the factors which drive evolution and change in the organisation in question. These criticisms have resulted in efforts being made to categorise MMs according to their application, this is discussed in more detail throughout the remainder of this chapter.

5.3 Maturity

The concept of *maturity* is mostly associated with the study of human psychology. A person's maturity can be defined as the ability to respond to the environment in an appropriate manner. Maturity models draw a connection between the concept of *maturity* from a human psychology perspective and organisational maturity via what is commonly referred to as 'organisational learning' (Van Dyk, 2013).

5.3.1 Organisational learning

Organisational learning is the act of growing in terms of maturity. The nature of maturity models implies that maturity is to some extent measureable across different states or levels. Maturity is not only about the current state, it also implies the transitioning from some initial state to a more advanced state. One of the primary aims of a maturity model is to assess the current state and to facilitate the transition across multiple states towards some predefined perfected end-state (Fraser *et al.*, 2002).

5.3.1.1 Organisational entity under consideration

Van Dyk (2013) identified three organisational entities which are typically measured through the use of a maturity model. The three entities within an organisational context are:

- **Process maturity** which refers to the extent to which a process is defined, managed, measured, controlled, and effective. The focus is on activities and work practices, with efficiency almost always being the underlying goal of process maturity;
- **Object or technology maturity** which refers to the extent to which a particular object or technology reaches a predefined level of sophistication; and
- **People or culture maturity** which relates to the extent to which the workforce can create knowledge and enhance proficiency.

5.3.2 Capability and maturity

The terms 'capability' and 'maturity' are often used interchangeably in literature. This can cause a great deal of confusion when discussing different types of maturity models. *Capability* is associated with specific business processes or a practice area within an organisation. Whereas, Van Looy *et al.* (2011) describe *maturity* as "the degree to which an organisation has explicitly and consistently deployed processes, according to the business objectives".

5.3.2.1 Capability levels and maturity levels

Capability levels are applied on a per process basis; whereas organisational maturity levels can be defined as a set of profiles for these processes (Paulk & Konrad, 1994). According to the CMMI Institute (2018) the maturity level or capability level of an organisation provides a way to characterise its capability and performance. Organisations should focus their improvement efforts on a prioritised and manageable number of practice areas at a time. Continuous improvement is something which all organisations should seek to embed in their culture. Maturity models assist organisations with linking their business objectives to the improvement goals they seek to achieve. By placing the focus of the organisation on achieving its business objectives with the help of a MM, performance results typically occur naturally and endure for longer.

A comparison between *capability levels* and *maturity levels* by the CMMI Institute (2018) is presented in Table 5.1.

Table 5.1: Capability levels vs. Maturity levels as described by the CMMI Institute (2018).

	Capability levels		**Maturity levels**
0	**Incomplete** Incomplete approach to meeting the intent of the Practice Area. May or may not be meeting the intent of any practice. **Inconsistent performance.**	**0**	Incomplete **Ad hoc and unknown** Work may or may not get completed.
1	**Initial** Initial approach to meeting the intent of the Practice Area. Not a complete set of practices to meeting the full intent of the Practice Area. **Addresses performance issues.**	**1**	Initial **Ad hoc and unknown** Work gets completed but is often delayed and over budget.
2	**Managed** Subsumes level 1 practices. Simple, but complete set of practices that address the full intent of the Practice Area. Does not require the use of organisational assets. **Identifies and monitors progress towards project performance and objectives.**	**2**	Managed **Unpredictable and reactive.** Projects are planned, performed, measured, and controlled.
3	**Defined** Builds on level 2 practices. Uses organisational standards and tailoring to address project and work characteristics. Projects use and contribute to organisational assets. **Focus on achieving both project and organisational peformance objectives.**	**3**	Defined **Proactive, rather than reactive.** Organisation-wide standards provide guidance across projects, programs, and portfolios.
4	**Quantitatively managed** Builds on level 3 practices. Uses statistical and other quantitative techniques to understand performance variation and detect, refine, or predict the area of focus to achieve quality and process performance objectives. **Identifies and understands variation, and predicts and improves the ability to achieve quality and process performance objectives.**	**4**	Quantitatively managed **Measured and controlled.** Organisation is data-driven with quantitative performance improvement objectives that are predictable and align to meet the needs of internal and external stakeholders.
5	**Optimizing** Builds on level 4 practices. Uses statistical and other quantitative techniques **to optimise performance and improvement to achieve quality and process performance objectives.**	**5**	Optimizing **Stable and flexible.** Organisation is focused on continuous improvement and is built to pivot and respond to opportunity and change. The organisation's stability provides a platform for agility and innovation.

5.4 Types of maturity models

According to Caralli *et al.* (2012) maturity models can be categorised as one of the following three types: *progression models*, *capability models*, or *hybrid models*.

Progression models represent simple, often linear progression of a practice, characteristic or attribute. The movement up the maturity levels correlates to the progression of the attribute's maturity. The levels describe higher states of achievement or evolution; they are typically agreed upon by the users, or industry experts. An example of a maturity *progression model* for counting is provided by Caralli *et al.* (2012):

A maturity progression for counting
Computer
Calculator
Adding machine
Slide rule
Abacus
Pencil and paper
Sticks and stones
Fingers

Here, the lower levels could be considered primitive, while the higher levels could be characterised as tool-enabled. Regardless of these characterisations it is important to note that progress does not necessarily equate to maturity.

The CMMI® as an example of a *capability maturity model* can be seen in table 5.1. Capability maturity models are more complex by nature than *progression models*, in that they are used to measure organisational capability around a set of characteristics, attributes, or processes. CMMs go beyond simply measuring the ability to perform a task, they also measure the extent to which capabilities are embedded into the organisational culture. This is the reason that CMMs describe the different states of organisational maturity relative to process maturity, as seen in table 5.1. The higher the degree of institutionalisation, the more stable those processes are, which equates to processes that are repeatable, consistent, and resilient during times of stress (Caralli *et al.*, 2012). The CMM framework developed by the SEI at Carnegie Mellon University has been used successfully in many cases and has also been built upon to provide more specialised frameworks such as the CMMI and the CERT-RMM (Computer Emergency Response Team - Resilience Management Model).

Hybrid models can be simply described as being a combination of *progression models* and *capability maturity models*, by combining the features of both types, *hybrid models* allow for the measurement of evolution as seen with *progression models* but with the added ability to measure capability, albeit not with the same level of rigor that the *CMM* allows for. Hybrid maturity models will have domains much like those of the other model types. However, the maturity levels of hybrid models will typically consist of defined sets of characteristics and outcomes, as well as capability considerations. The content of the model will be attributes, characteristics and processes which represent progression, and capability, as opposed to just one or the other.

The benefits of using *hybrid models* include ease of use, easy measurement of core competencies and an approximation of capability.The primary drawback of using a hybrid model is that the same level of rigor when measuring capability can not be achieved as when the CMM is used.

5.4.1 Descriptive, prescriptive, and comparative models

Pöppelbuß & Röglinger (2011), Becker *et al.* (2009) and De Bruin *et al.* (2005) differentiate MMs by categorising them according to their application. The following three categories are described: *descriptive models*, *prescriptive models*, and *comparative models*.

Descriptive models provide an organisation with a diagnostic tool, with which it can perform internal, external, and longitudinal benchmarking. *Prescriptive* models typically draw from historical data to enable an organisation to develop a road-map for improvement measures (De Bruin *et al.*, 2005). Pöppelbuß & Röglinger (2011) describes the third type of model as being *comparative*. Comparative models allow for benchmarking to be performed by organisations with similar practices and process across different industries and regions. De Bruin *et al.* (2005) likens each of these three models to different phases of an evolutionary life cycle. Descriptive models have value when seeking to attain a deep understanding of the 'as-is' state, which after multiple instantiations, evolves to become a prescriptive model. Finally the model can be considered comparative when it has matured to the point that it can be applied in a wide range of organisations and across multiple industries.

5.5 Essential components of a maturity model

Although various MMs can differ significantly in type or purpose, most MMs conform to a set of basic structural components. It is important to understand this structure as it provides the user with important linkages between the objectives, assessments, and best practices; as well as between the current capabilities and the improvement roadmap, linking business goals, standards, and so forth. In this section, the relevant terminology as it relates to this study

will be defined. Unfortunately there is a significant amount of confusion and incorrect use of terminology in the literature (Van Dyk, 2013).

Levels

Levels represent the transitional states in the maturity model. Depending on the purpose of the model and the domain in question, a level could represent an expression of capability or some other attribute which can be measured by the model. These levels have been discussed in more detail in Section 5.3.2.1.

Domains and attributes

A *domain* is a group of attributes which are collectively considered as an area of importance for the subject matter and intent of the model (Caralli *et al.*, 2012). Van Dyk (2013) provides a suitable definition of a domain which can be used for the purpose of this study: "A domain is a sphere of activity, concern, or function and represents an angle from which to view the use, consequences and implications of the entity under consideration". According to the CMMI Institute (2018) the CMMI® Development V2.0 refers to domains as 'practice areas', where they formerly referred to domains as 'process areas'. The reason for this change was to emphasise that CMMI® Development V2.0 is a collection of best practices, rather than just a set of processes to be implemented.

Attributes represent the core content of the model grouped together by domain and level (Caralli *et al.*, 2012). Attributes are typically based on processes, observed- and best practices, and standards.

Diagnostic methods

A useful maturity model must include some mechanism for assessment, measurement, gap identification, or benchmarking.

Improvement roadmaps

As previously stated, most maturity models tend to serve two purposes, a descriptive role for the purpose of benchmarking, followed by a prescriptive role for the purpose of outlining an improvement initiative moving forwards. This cycle can be likened to the classic plan-do-check-act cycle.

5.6 Interoperability

The Healthcare Information and Management Systems Society (2017) defines interoperability within a healthcare context as "the ability of different information technology systems and software applications to communicate, exchange data, and use information that has been

exchanged". HIT interoperability can be further broken down into four levels: *foundational*, *structural*, *semantic*, and *process*.

Foundational interoperability involves data exchange between two information technology systems where the system receiving the data does not necessarily possess the ability to interpret the data. *Structural* interoperability involves the use of data exchange standards, or standard message formats (the ICSR discussed in Chapter 4 is an example of this). The use of these data exchange standards ensures that when there is uniform movement of health data from one system to another, the clinical or operational purpose and meaning of the data is preserved and unaltered. *Semantic* interoperability is the highest level of interoperability, this is achieved when two or more IT systems can exchange information and make sense of that information (Healthcare Information and Management Systems Society, 2017). *Process* interoperability refers to the coordination of business processes at an organisational level. Process interoperability is achieved when human beings share a common understanding of the business processes (Soceanu *et al.*, 2013).

According to Gottschalk (2009), interoperability results as a product of standardisation in four dimensions: *technology*, *syntax*, *semantics*, and *pragmatics*. Technology standards concern the technologies involved which make up the system, together with networking protocols and security protocols. Syntax standardisation refers to the agreement on the structure and language of the messages exchanged between the various heterogenous applications across the network. With reference to the preceding discussion of levels of HIT interoperability, syntax standardisation enables structural interoperability. Semantic standardisation enables semantic interoperability of HITs. Finally, pragmatic standardisation refers to agreements on protocols and practices which are prompted by specific messages.

Hammond *et al.* (2010) provide four axioms of interoperability for health information systems:

1. Data should be entered only once and should be available for multiple purposes, that is, they should be 'reusable.'

2. Interoperability requires the cooperation of a group of stakeholders to ensure the application of consistent rules across technical domains. It must also be done with sensitivity to legal, ethical, and societal requirements, including security, privacy, and confidentiality.

3. A single global set of data elements with attributes must become the building blocks of all such systems. Precise and unambiguous definitions of items are mandatory.

4. There will be diverse health information systems, not just one or even several – it is critical to achieve interoperability among all of them.

The potential impact of interoperability should not only be considered in terms of the current state of the healthcare delivery system. The potential future benefits of interoperability could be truly significant, especially when one considers the impact that interoperability could have on easing the load on health information exchanges imposed by the development of future healthcare technologies such as EHRs (Brailer, 2005). There are typically two schools of thought when considering interoperability and its association with the attempted introduction of a new interoperable system. The first suggests that interoperability should precede the development of the system itself, that is to say that the ability to share information should be designed into the system from the onset of development. The second school of thought is that interoperability follows naturally after widespread adoption of stand-alone systems, as a result of the natural evolution of standards.

5.6.1 Interoperability and EHRs

The most widely covered topic in literature when it comes to eHealth and interoperability is the EHR (Erturkmen *et al.*, 2011). The primary limitation of EHR mining for pharmacovigilance data is that the data in EHRs is not collected for the purpose of PV activities such as signal detection. Erturkmen *et al.* (2011) suggest the use of EHRs to improve post-marketing safety activities on a proactive basis. The ability to mine EHRs for data will constitute a partial solution to the largest problem facing spontaneous reporting systems, underreporting. Functional and semantic interoperability would enable secondary use of EHR data in an efficient and effective way to reinforce post-marketing safety studies. Interoperability means that pharmaceutical companies and regulatory authorities can cooperate during post-marketing safety studies even though the data exists in heterogeneous, distributed EHR systems.

Successful integration of EHR data will directly improve post-marketing safety activities by allowing automated ADE detection tools to screen hospital EHRs, thereby eliminating the need for manual screening of patient medical records and thus easing the burden on HCPs. Extraction of relevant data directly into an ICSR reduces errors associated with the double entry of data, as well as reducing lead times when transmitting ADE data to regulatory authorities. Along with these benefits, the use of interoperable EHRs would significantly improve on current ADE detection capabilities by allowing the monitoring of multiple, distributed, heterogeneous EHR systems (Erturkmen *et al.*, 2011). EHRs also facilitate the monitoring of patients over extended periods of time and thus contribute to improved monitoring of a medicine's effectiveness and outcomes over the entire life cycle of the medicine and/or the patient.

Brailer (2005) provides reasons as to why achieving interoperability within an eHealth context could be challenging. The study likens the introduction of EHRs to that of the fax machine, the last to install an interoperable EHR benefits significantly from the prior investment of everyone else, while the first to install incurs most of the costs. The overall aim of interoperability is to provide benefits across a wide range of stakeholders. Unfortunately, along the path to interoperability, some stakeholders are bound to lose due to the disruption of long-standing industry practices. Furthermore, early adopters experience what is known as the first-mover disadvantage[1].

To date, the largest project involving EHRs in post-marketing safety studies has been the SALUS project also known as the "Scalable, Standard based Interoperability Framework for Sustainable Proactive Post Market Safety Studies" (Erturkmen *et al.*, 2011). The project budget was €5.077 million and its main objective was to provide a comprehensive solution to enable the secondary use of the already available EHR data in the patient care domain, for clinical research purposes. SALUS particularly aimed to strengthen the spontaneous reporting process by automating ADE detection across disparate EHR systems. Hammond *et al.*'s (2010) third axiom of interoperability was a focal point of the SALUS project's efforts, with harmonised ontologies acting as a common denominator for the exchange of clinical data (Erturkmen *et al.*, 2011). It is important to note that the operationalisation of the solution offered by the SALUS project in any given context will be dependent on the large-scale roll-out of EHRs in the context.

Erturkmen *et al.* (2011) discusses the five main challenges faced when seeking semantic interoperability among heterogeneous knowledge sources in the healthcare domain. These five challenges are: (i) *context-awareness*: the ability to identify context-specific components from various knowledge sources relevant to the clinical problem at hand; (ii) *modularity*: the ability to reuse relevant components from various knowledge sources; (iii) *profile and policy management*: the ability to treat internal policies or profiles distinctively; (iv) *correspondence expressiveness*: the ability to relate heterogeneous knowledge, within or between changing contexts; and (v) *dealing with inconsistencies*: patching or tolerating discrepancies, incompatibilities, and inconsistencies, within or between contexts.

[1] *"The mechanisms that benefit the first-mover may be counterbalanced by various disadvantages. These first-mover disadvantages are, in effect, advantages enjoyed by late-mover firms. Late-movers may benefit from: (1) the ability to 'free-ride' on first-mover investments, (2) resolution of technological and market uncertainty, (3) technological discontinuities that provide 'gate-ways' for new entry, and (4) various types of 'incumbent inertia' that make it difficult for the incumbent to adapt to environmental change" (Lieberman & Montgomery, 1988).*

5.6.2 Interoperability and maturity models

A maturity model which aims to promote and improve interoperability should seek to address the degree of integration of systems involved, provide guidance on which system components need to be improved, as well as provide a means for measuring interoperability progress in a community. Interoperability can be complex when dealing with multiple large systems, it can also be difficult to define because while interoperability can be measured to some extent, it is not a entity in and of itself. Interoperability can be measured by assessing how diverse entities interact and work together across technical, social, political, and organisational boundaries.

Gottschalk (2009) proposed a maturity model for e-Government interoperability. Gottschalk (2009) considered the nine constraints laid out by Scholl & Klischewski (2007) that influence government integration and interoperability. In this research it is useful to consider seven of these constraints, with the constitutional and jurisdictional constraints being excluded from further discussion. The seven constraints considered are as follows (Gottschalk, 2009):

1. **Collaborative constraints**: Organisations differ in terms of readiness and capability for collaboration and interoperability. Organisational leadership style will influence the organisation's degree of willingness for and acceptance of potential interoperability.

2. **Organisational constraints**: Without the standardisation of processes, systems, and policies, achieving interoperability could prove to be exceedingly difficult.

3. **Informational constraints**: Organisations may be unwilling to share certain types of information. Difference in opinion as to what constitutes transactional, strategic, or organisational information could result in resistance to the sharing of information. Quality issues could also arise as a result of heterogeneous systems built upon differing data and quality standards.

4. **Managerial constraints**: Interoperability becomes more difficult to achieve as the number of organisations involved increases. Organisations may also have in-congruent interests, needs, and perspectives.

5. **Cost constraints**: Although information sharing initiatives and interoperability are typically associated with a reduction in cost, interoperability between multiple organisations could be limited to the lowest common denominator in terms of availability of funds.

6. **Technological constraints**: Similar to the cost constraint, interoperability between multiple organisations could be limited to the lowest common denominator in terms of technological capability. Although, with the increase in heterogeneous health information systems across the world, interoperability could arise as a product of the increased adoption of higher standards.

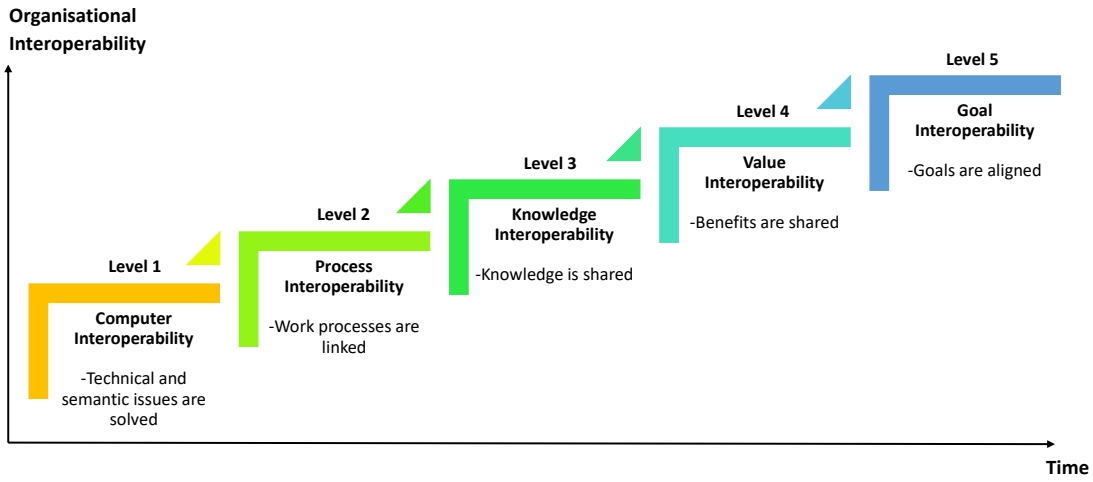

Figure 5.1: Maturity levels for interoperability in e-Government. Adapted from Gottschalk (2009).

7. **Performance constraints**: The overall system performance in terms of responsiveness decreases with the higher number of interoperating system participants.

Together with these constraints Gottschalk (2009) provides a set of maturity levels for the interoperability of e-Government. The levels, shown in Figure 5.1, are defined in such a way that they focus on semantic interoperability and organisational interoperability. Organisational interoperability is defined as the extent to which organisations using different work practices are able to communicate (Gottschalk, 2009).

Level 1 - Computer interoperability

At this level interoperability is achieved when the appropriate hardware and software systems allow for semantic information sharing. Semantic interoperability refers to the ability to directly exchange messages, as well as meaningful, context-specific data between two or more IT systems.

Level 2 - Process interoperability

At this level work processes are aligned between organisations so as to achieve interoperability. It is important to consider that work processes are adopted by the organisation as well as the person carrying out the work process.

Level 3 - Knowledge interoperability

Electronic work processes deal with information but knowledge work is handled by employees in collaborating organisations. Gottschalk (2009) proposes that knowledge sharing is critical to

the maintenance of good relationships between organisations and plays a vital role in resolving issues relating to incompatibilities across a network of information systems.

Level 4 - Value interoperability

A value network is an organisational value creation configuration similar to the more frequently studied value chain. A value network generates value through the efficient connection of subscribers to the network. Interoperability at this levels is concerned with interactions between primary activities in different value configurations that exist in the healthcare industry.

Level 5 - Goal interoperability

Gottschalk (2009) states that the role of IT functions is to support and influence organisational strategy. At this level of interoperability, organisations have no competing goals, which is often the case in the lower levels of the model.

The model proposed by Gottschalk (2009) includes a cautionary statement that the optimal level of interoperability is not necessarily the highest level in their maturity model. From a cost perspective it is important to consider the cost of transacting between systems and the volume of transactions. If the volume of transactions is low or the cost of transacting high, it may be wasteful to seek comprehensive strategic alignment (goal interoperability) between interoperating organisations. An example of an interoperability maturity model in the HIT field is the one that was proposed by van Velsen *et al.* (2016) and deals with interoperability in an eHealth context. van Velsen *et al.*'s (2016) proposed maturity model for the interoperability of eHealth systems, can be seen in Figure 5.2. It is intended to guide the development of an interoperable eHealth infrastructure.

Although maturity models exist for enterprise interoperability and e-Government interoperability, the case of eHealth poses a unique set of challenges which differentiates it from the former cases. In an eHealth context there are different actors such as patients and healthcare professionals who interact and form part of different organisations such as medical institutions, commercial companies, or government bodies, each of these organisations having distinct protocols, information needs and information systems. Stroetmann (2014) defines interoperability in eHealth as "facilitating and safeguarding the exchange, understanding, and acting on patient and other health information and knowledge among linguistically and culturally dispersed medical professionals, patients, and other actors within and across healthcare systems in a collaborative manner".

The levels of interoperability in van Velsen *et al.*'s (2016) maturity model are discussed below and take into consideration interoperability from a *technical* point of view, its implications for working *procedures*, and the role of *standardisation* in interoperability.

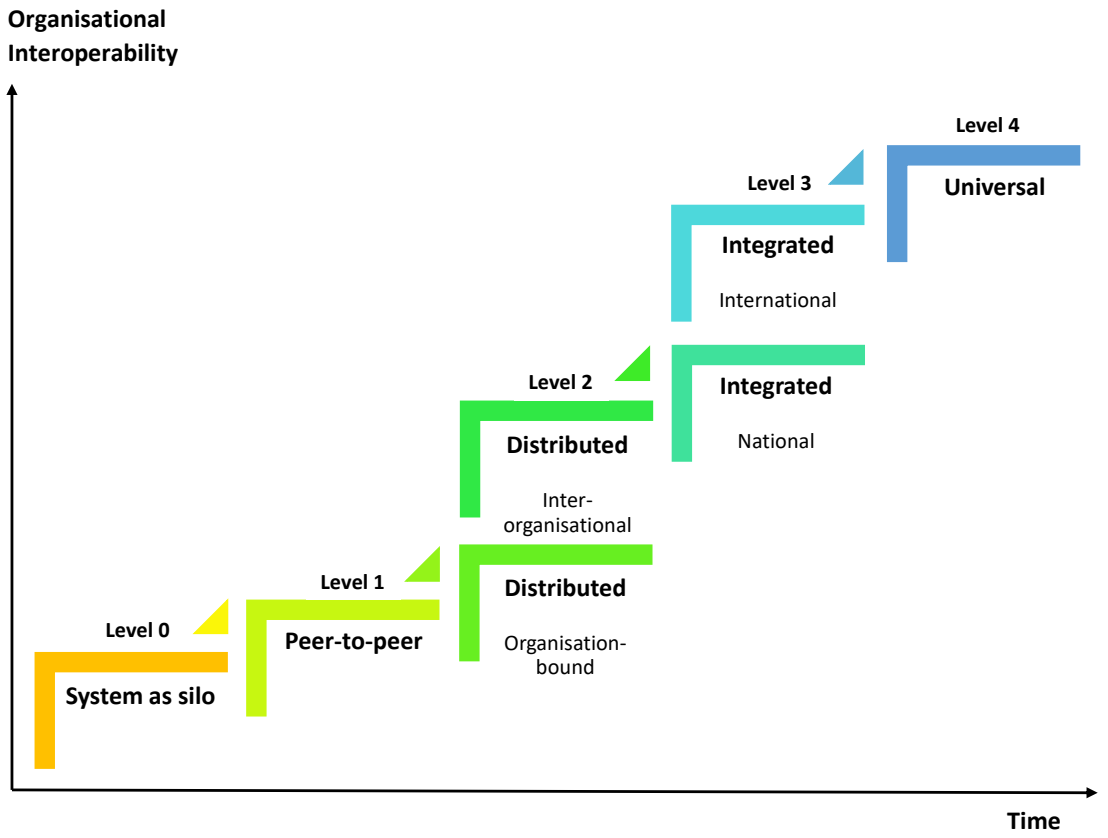

Figure 5.2: Maturity levels for interoperability in eHealth. Adapted from (van Velsen *et al.*, 2016).

Level 0 - System as a silo

Technical. An eHealth application consisting of a single technology, not connected to any other application.

Procedural. This application does not change the nature of the task that it is supposed to serve, and does not necessitate the redesign of any protocols or medical procedures.

Standardisation. No standardisation is required as a single eHealth application does not require the means to communicate with other technologies.

Level 1 - Peer-to-peer systems

Technical. Two applications directly linked to one another for simple data exchange.

Procedural. The transfer of data occurs in a context where the parties involved have made simple agreements about a working procedure.

Standardisation. Both systems should take into consideration agreements on how to exchange data as well as the format of the data. Data handling before and after transmission is left to the discretion of each of the system's users/developers.

Level 2 - Distributed systems

Technical. Linking of eHealth applications to achieve a common objective. Server architecture is used in such a way so as to allow multiple applications to communicate with each other via a central service. At first, the different applications are provided under control of one supplier (distributed, organisation-bound). The next step is to cross the organisational boundary and to link applications of different suppliers for achieving a common objective (distributed, inter-organisational).

Procedural. At this level of interoperability, the streamlining of protocols and organisational procedures is a necessity. The interoperable infrastructure should support the varying protocols and working routines of the actors across the different organisations, as much as possible. For working procedures that are non-conclusive or contradictory, a new, shared procedure must be found as a solution and incorporated into the interoperable infrastructure.

Standardisation. At this level it is important to consider how data is exchanged between organisations with special attention to data safety, security, and privacy standards. Standards development organisations such as HL7 have produced extensive resources for health information exchange standards. Standards at this level also seek to ensure semantic interoperability among heterogeneous organisations.

Level 3 - Integrated systems

Technical. At this level of interoperability, applications from different suppliers that serve a common goal are linked, but the applications do not need to have common objectives. The infrastructure is developed to offer interoperability to a selected set of eHealth suppliers either on a national level (integrated, national) or on an international level (integrated, international). The set of suppliers may shrink and expand over time but it is never intended to be 'open for all'.

Procedural. At this level of interoperability it becomes difficult to streamline procedures as the possibilities that eHealth technologies offer become paramount. No protocols or organisational policies exist to guide such widespread exchange of data. Instead, this level of interoperability should encourage the discovery of new use cases and allow applications to play a supportive role, which may lead to the adaptation of existing protocols. This provides a useful means of re-assessing how healthcare is organised.

Standardisation. Standardisation at this level does not differ significantly from the previous level. The same standards and terminologies are used to facilitate the smooth exchange of data among the applications in the eHealth infrastructure.

Level 4 - Universal interoperability

Technical. At this level of interoperability the infrastructure allows for applications to connect and disconnect freely, making use of data exchanges without having to serve a common goal, and also while spanning multiple countries.

Procedural. Similarly to the case in Level 3, this kind of interoperability allows for supporting existing work procedures and protocols as well as for many new use cases. The availability of data at this level of interoperability provides ample opportunity for data mining and possibly the introduction of new insights and use cases.

Standardisation. Standardisation at this level does not differ significantly from the previous level. The same standards and terminologies are used to facilitate the smooth exchange of data among the applications in the eHealth infrastructure.

van Velsen *et al.*'s (2016) maturity model shows how an eHealth application can evolve from a stand-alone entity to a part of a universal network for eHealth. The model can be used for benchmarking a set of applications or infrastructures with regard to their level of interoperability, or as a roadmap for developing interoperable eHealth infrastructure.

5.7 The need for a sociotechnical approach

Both Gottschalk (2009) and van Velsen *et al.* (2016) concluded that in order to achieve inter-organisational interoperability one must consider the appropriate sociotechnical characteristics of the organisations involved. For interoperability to be achieved between various heterogeneous information systems, it is clear that some organisations will have to adapt their technical and organisational processes to accommodate the standardisation initiatives. Challenges relating to interoperability from a technical perspective are more easily understood, however, it is perhaps of greater importance to understand the challenges brought about from an organisational perspective. Interoperability can result in the creation of new work processes, the mobilisation of limited resources, and the management of inter-organisational relationships (Pardo & Tayi, 2007). These changes are products of specific social interactions such as group decision-making, trust building, and conflict resolution. These dimensions form part of the greater discussion on sociotechnical systems, which is discussed in detail in Chapter 6. Chapter 6 provides an argument for the adoption of a sociotechnical systems design approaches to improve the design, implementation, and adoption of HITs which seek to assist in promoting safer, better healthcare. The need to incorporate the social sciences in the improvement of health information systems (HIS) has been widely acknowledged in literature, however, it has not yet been realised through the application of conventional system design methods in the context of PV (Braithwaite *et al.*, 2009).

5.8 Chapter 4: Conclusion

In this chapter the concept of an MM was explored and defined within the context of this study. The history of MMs as well as their various types and purposes was discussed. The concept of interoperability was discussed, with a particular focus on the interoperability of HITs in the eHealth field. The chapter concludes with a discussion on the need to include a sociotechnical approach to introducing MMs within an eHealth context.

Chapter 6

A sociotechnical system perspective

Taking into consideration the difficulty associated with implementing standardised HITs into large, complex systems, the notion of a sociotechnical system is investigated in this chapter. The need for a sociotechnical approach to studying HITs in complex adaptive health systems is explained and motivated. A comparison is drawn between a generic sociotechnical system and the PV system across multiple levels of analysis, in an attempt to better understand how sociotechnical systems design methods can lead to systems which are more acceptable by- and provide better value to all stakeholders of the system.

The contents of this chapter form part of the conference proceedings titled "Sociotechnical considerations for HIT design and implementation in complex and adaptive health systems" which was presented at the 27th annual conference of the International Association for Management of Technology (IAMOT), held from 22 - 26 April 2018 at Aston Business School in Birmingham, United Kingdom.

> "If we want safer, higher-quality care, we will need to have *redesigned systems of care*, *including* the use of *information technology* to *support clinical* and administrative processes" (Corrigan *et al.*, 2005).

6.1 Introduction

The activities relating to PV form part of what is essentially an extended health system-wide quality management system (Santoro *et al.*, 2017) that contributes towards patient safety. Patient safety relies on data systems and data systems rely on data standards. Traditional approaches to introduce information and communications technology (ICT) into complex systems have been plagued with multiple shortcomings. This has highlighted the need for an alternative approach.

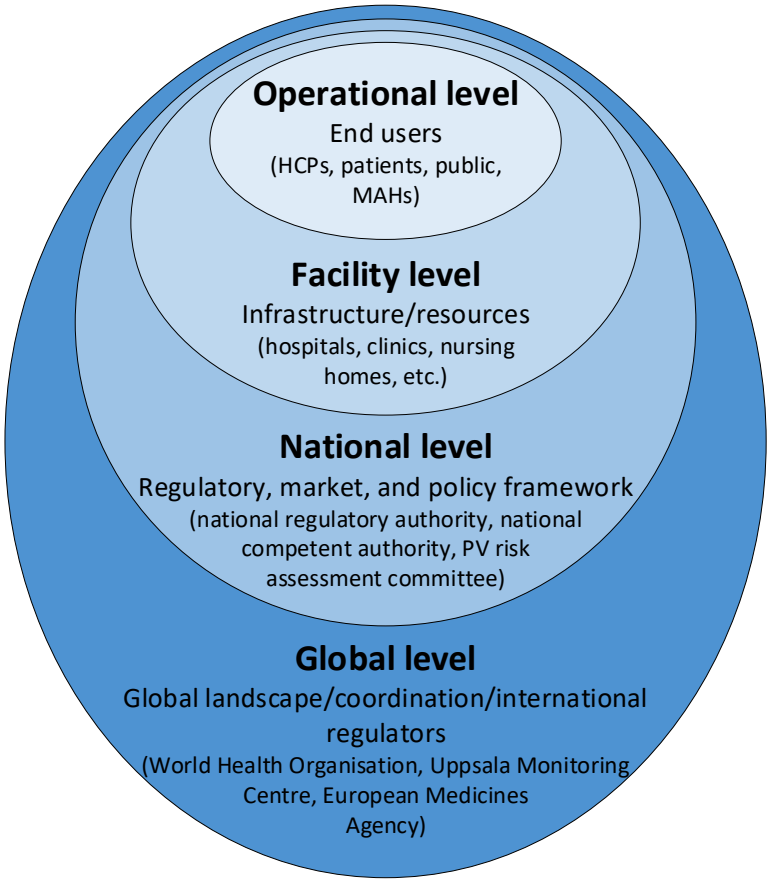

Figure 6.1: A conceptual diagram of a four-level health system.

6.1.1 Level of analysis

The activities relating to PV can be associated with different levels of a health system. The functions of a PV system are carried out by different people, in different physical environments, working under different organisational structures, with different responsibilities, across these different levels of the healthcare system. The scope of this research revolves around the first stage of the PV system that is, the reporting of ADRs, and the subsequent propagation of the generated signal to the VigiBase system of the World Health Organisation. With this in mind, the four levels in Figure 6.1 will be explained briefly:

1. *Operational level:* From an engineering perspective, the operational level of a system is the level at which decisions relating to the day to day activities of an organisation are made. Spontaneous reporting of suspected ADRs is the cornerstone of pharmacovigilance in that it generates the largest amount of data. It is at the operational level where the HCPs and patients have a direct interaction with the HIT system. At this level the nature

of healthcare work and the individual characteristics of the HCPs, such as knowledge base, skill level, training and education, attitudes, beliefs, and physical capabilities have the largest influence on the success or failure of the system.

2. *Facility level:* The facility level encompasses the operational level. The facility within which the HCP works will have a number of intrinsic characteristics, such as the physical environment and layout, the organisational structure, embedded human-system interfaces, communication and coordination practices, as well as local work procedures.

3. *National level:* All facility level activities are governed and coordinated at the national level. Each country conducting PV activities will do so according to different healthcare policies, laws and regulations. Decisions made at this level have a trickle down effect onto the facility and operational levels, affecting the overall safety, quality, and efficiency of these parts of the larger system. The PV data generated at the preceding levels is collated and analysed internally by NCAs before transmitting the signals to the VigiBase system.

4. *Global level:* At the global level there are a number of external environmental forces influencing the system, such as technological innovations, economic pressures, political climate, and public awareness. The global level is unique in the context of a PV system in that participatory countries submit their domestic PV data to the World Health Organisation for the benefit of the entire worlds population.

Based on these descriptions of the levels of the healthcare system, it becomes clear that the outcome of patient care is produced through the interaction of multiple intricate and fragmented subsystems. This view of a health system highlights the need to educate HCPs across all levels and make them aware of their functioning in the greater system (Hartman *et al.*, 2017).

6.2 Introduction to systems engineering and sociotechnical systems

A system is a purposeful collection of inter-related components that work together to achieve a common objective. A system may include software, mechanical, electrical and electronic hardware (Sommerville, 2004). People, and the respective organisations to which they belong, are responsible for the systems entire development life cycle, including its operation and ownership. The properties of these systems are most often inextricably inter-mingled, which can lead to high degrees of complexity. The behaviour of complex systems is often very difficult to predict. This represents the largest challenge that is faced by organisations which seek to

develop, leverage, and control complex systems to improve their operations and activities. In the case of PV this relates to the introduction of health information technologies to support the functioning of SRSs and improve interoperability across the global PV system.

Systems Engineering is an interdisciplinary field of engineering which comprises the body of knowledge concerned with the design and management of complex systems throughout a system's life cycle. In the early years of systems engineering the general consensus was to take a technocentric[1] approach to systems development, this approach has been challenged by the introduction of a relatively new body of knowledge known as Sociotechnical Systems Engineering (STSE). A sociotechnical system (STS) is one which includes technical systems but also operational processes and people who use and interact with the technical system.

STSE places more importance on a user-centred approach; one which focusses more so on job satisfaction and the needs of the end user. The use and value of sociotechnical systems design methods is discussed in more detail in Section 6.2.2. As with systems engineering and its focus on the end user, the activities related to PV are patient centred. It can be argued that every actor involved in the PV system is an end user in that every actor extracts value from, and interacts with, the system in a different way. A sociotechnical approach to studying systems places special attention on the interactions and interdependencies of the system components, not only on the components themselves.

6.2.1 The sociotechnical nature of healthcare work

Health information technologies (HITs) such as EHRs, computer physician order entry, and clinical decision support systems are those which leverage computer systems to improve safety and quality of care, while assisting in cost reduction and improved efficiencies. Difficulties faced by those using these HITs have been widely described as being 'organisational issues' (Berg, 1999). When designing information technology solutions for health systems it is important to acknowledge that health care work has an inherent 'ad hoc' and 'Byzantine'[2] nature; and that many attempts to use IT initiatives in a health care context have failed due to incompatibility between organisational issues and the structured, standardised and rational nature of IT systems (Berg, 1999).

A common challenge in implementing HITs is to move from the drawing board to successful implementation. HITs are too often bound to the specific context within which they have been developed (Berg, 1999). When designing a new HIT system, it is clear that a sociotechnical

[1] Technocentrism is a value system rooted in classical science, technology, conventional economic thinking, and in the human control over nature.

[2] (of a system or situation) excessively complicated, and typically involving a great deal of administrative detail.

design approach can hold significant value, the nature of healthcare work is inherently messy and is the goal of protecting the health of a patient is often realised through a collaborative effort between many HCPs across multiple healthcare disciplines. With the introduction of a new technical system, one must be sensitive to the fact that the system will become so intertwined with the work environment in which it exists, and that each change in IT will have widespread consequences for that work practice (Berg *et al.*, 1998).

Sociotechnical approaches focus on the nature of health care work and working with information technologies as a social process. Patients have varying needs and present various problems to the healthcare professionals seeking to care for them. Standard organisational solutions never wholly fit a patients individual problem.

Studies in cognition show that what we traditionally conceive as individual thinking processes are in fact heavily influenced by the social and physical contexts within which these thinking processes take place (Hutchins, 1995). With new technologies enabling new forms of communication between health care workers, the relations between those communicating are invariably affected. When communication between health care workers becomes more efficient, the delivery and quality of patient care is improved.

6.2.2 Sociotechnical systems design

STSE is an approach to systems design which considers human, social, and organisational factors with equal importance to that of technical factors (Baxter & Sommerville, 2011). Adopting a sociotechnical approach to systems development results in systems which are more acceptable to end users and deliver better value in the organisations within which they exist. A sociotechnical approach to organisational change, such as in the case of implementing new ICTs in healthcare systems, focusses on two key activities, those being sensitisation and awareness, and active engagement of all relevant stakeholders (Berg *et al.*, 1998).

The aim of taking a sociotechnical approach to system design and the implementation of new technologies in a healthcare environment should seek to improve the traditional way of carrying out the primary care process. The largest challenge and simultaneous largest opportunity with regard to this is to find a synergy between the formal tools of information technology and the sociotechnical nature of healthcare work.

Technological innovation can be seen as a social process in which organisations are deeply affected (Baxter & Sommerville, 2011). Insights from the social sciences are becoming increasingly recognised within the field of health informatics and information systems in general. Information systems require human interaction and input, resulting in both elements of the system affecting each other. To understand these affects, the interrelation between technology

and the social context of its use must be studied accordingly. Taking a sociotechnical approach to systems design aims to accomplish exactly that. Sociotechnical approaches seek to understand the way in which information technologies are developed and implemented, as well as how these systems become a part of social practices. In the simplest way, sociotechnical approaches seek to strike a balance between the social, environmental, and technical elements of a system so as to develop users skills and to improve job satisfaction and working relationships (Berg *et al.*, 2003).

Technological development cannot be seen as a merely technical linear process. Upon uncovering how the introduction of new technologies impact the work setting in which they have been implemented, one can investigate the feasibility of the social roles that are inscribed in the system for the working environment.

The process of developing the technology is of paramount importance. A sociotechnical approach to the development process favours the central role of the user, however, involving the user is not often as easy as it might seem. The design approach should embrace the non-linear nature of technology development and allow for iterative and incremental improvement to be made in the system. Instead of aiming to design the perfect system before implementation, the design approach must allow for more flexibility, involving the stitching together of partially integrated systems which would better satisfy the information needs of a complex organisation (Monteiro *et al.*, 2003). Sociotechnical systems exhibit emergent properties, in that some of the properties of the system only emerge after it has gone into use and cannot be predicted in advance (Baxter & Sommerville, 2011). This is true of all systems but in particular sociotechnical systems because of the complexity of the interactions between parts of the system.

From a sociotechnical perspective, design is about finding the synergy between specific characteristics of healthcare work, and the potential benefits of ICT. It is about designing interactions not from the view of the technology but from the users that work with that technology, and the practices in which it will become embedded (Berg *et al.*, 2003). The emphasis should be on guiding and nurturing the natural properties of sociotechnical systems rather than imposing top-down instructions and hierarchical structures from people who do not actually work at the operational level (Braithwaite *et al.*, 2009).

As stated previously, the activities relating to PV occur at different organisational levels throughout the health system. Most systems engineering approaches to improve PV fall short of their goals, by merely focussing on the lower levels of the of the system. Although it is clearly important to focus on the point of patient care, one must not forget to consider the multitude of other influential factors at higher organisational levels. The STS design approach allows

for more cognisance of failures originating from different levels of the system. Active failures are characterised as being those resulting from the decision of an individual, in the context of PV this could be an incorrect dosage delivery, choice of drug, or route of administration. These types of failures are typically found in, and constrained within, the lower levels such as the operational level. Latent failures are those which manifest as a culmination of small inefficiencies and flaws in the higher levels of the system, flaws and inefficiencies which have a trickle down effect on the lower levels. In terms of PV this could be the effects of national policies and the way in which these policies are implemented on an operational level. Another example of a latent failure is the inadequate education and training of HCPs with regard to PV activities.

Figure 6.2 shows the layers that make up a typical sociotechnical system. When comparing this figure with the discussion on the levels of analysis in Section 6.1.1, one can see how the operational level encompasses the majority of the lower levels of the sociotechnical system stack.

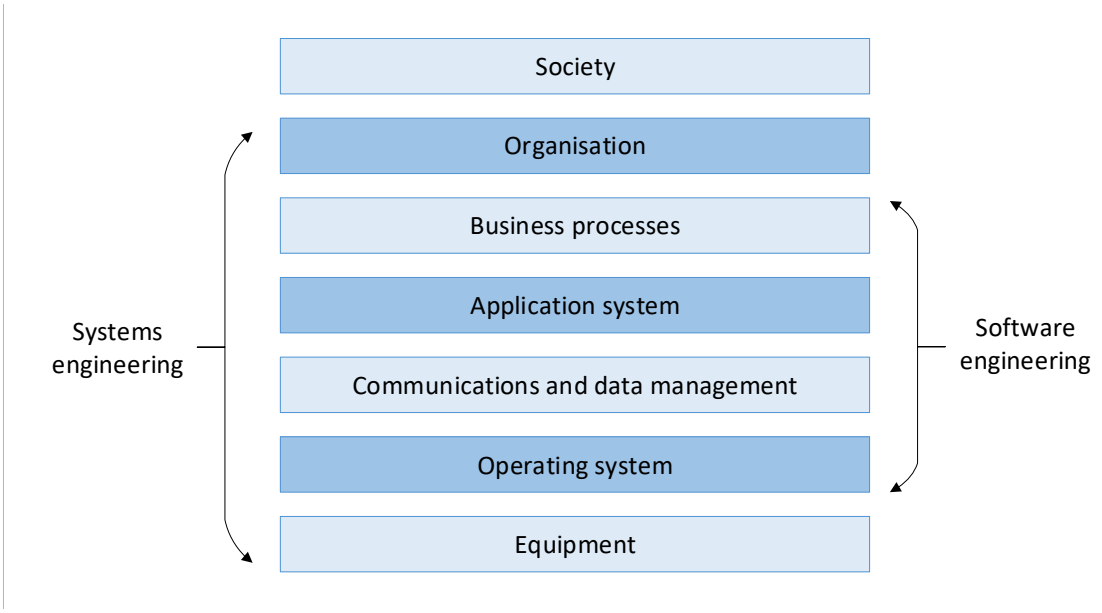

Figure 6.2: Layers of a sociotechnical system stack.

6.3 Pharmacovigilance as a sociotechnical system

Considering the sociotechnical nature of healthcare work as discussed in Section 6.2.1, one can classify the PV system as a sociotechnical system. Sociotechnical systems include IT systems and the social and organisational environment in which these systems are used.

6. A SOCIOTECHNICAL SYSTEM PERSPECTIVE

Badham *et al.* (2000) defines five characteristics of open sociotechnical systems:

1. Systems should have interdependent parts;
2. Systems should adapt to and pursue goals in external environments;
3. Systems have an internal environment comprising separate but interdependent technical and social subsystems;
4. Systems have equifinality. In other words, system goals can be achieved by more than one means. This implies that there are design choices to be made during system development; and
5. System performance relies on the joint optimisation of the technical and social subsystems.

PV can be classified as an open sociotechnical system according to the five characteristics defined by Badham *et al.* (2000). Healthcare professionals interact with hardware and software infrastructure, recording, storing, and sharing data through the use of a human computer interface. These actions coupled with the multidisciplinary nature of communication and work flows in healthcare, influence internal organisational policies and culture, while adapting to ever changing external environments such as rules and regulations (Sittig & Singh, 2010).

The aim of this chapter is to provide an argument for the adoption of a sociotechnical systems design approaches to improve the design, implementation, and adoption of HITs which seek to assist in promoting safer, better healthcare. In the case of PV, this would involve the HITs which are designed to support the processes relating to the spontaneous reporting of ADRs, and improved interoperability of SRSs. As mentioned in Section 5.7, the need to incorporate the social sciences in the improvement of health information systems has been widely acknowledged in literature, however, it has not yet been realised through the application of conventional system design methods in the context of PV (Braithwaite *et al.*, 2009).

Individual users from different small work groups (GPs, nurses, pharmacists, etc.) in the PV system, will inevitably interact with these HITs in different ways. Certain features of the HITs will be appropriated by some but rejected by others, this relates to the common uncertainty between HCPs regarding where their individual responsibilities begin and end within the system. To understand how technology changes the work practices of HCPs, an investigation into what HCPs understand about the technology, and how they use technology in their daily work practices, should be conducted. An important consideration that is often overlooked is to study not only the adoption of new technology but also its rejection. This must be carried out with the use of qualitative research methods during the implementation and evaluation stages of

the project life-cycle. Ethnographic[1] studies, after the implementation of HITs such as those supporting the spontaneous reporting of ADRs by HCPs, must be carried out to understand how they perform their work functions *in situ*[2] (Petrakaki *et al.*, 2010).

Research by Cho *et al.* (2008) shows how the adoption of HIT in a hospital resulted in a redistribution of professional responsibility as well as a redistribution of labour as people tried to inscribe their interests into the technology. The research further showed that physicians were reluctant to adopt the new paperless information system as they believed it would project extra administrative duties onto themselves, which they had previously informally displaced to nurses. Nurses on the other hand embraced the technological change process as they felt they would have increased control over the monitoring of their patients. This is an example of how different users experience the adoption process differently, which can have varying influence on the design, development and use of the systems.

Studies on human factors and ergonomics relating to patient safety carried out by Safren & Chapanis (1960) found that the majority of medication errors were largely due to work system factors such as failure to follow required protocols and procedures, as well as verbal or written communication problems. The medication errors were categorised as: (i) wrong patient; (ii) wrong dosage; (iii) extra unordered medication; (iv) omitted medication administration; (v) wrong medication; (vi) wrong timing of medication administration; and (vii) incorrect route of administration.

HCPs work more efficiently when allowed to perform work in an autonomous manner, rather than being directed, micromanaged and controlled through a hierarchical structure. A bottom-up strategy is urgently needed to counter the traditionally top-down approaches which only result in modest improvements that are typically difficult to sustain. Healthcare reformation must be championed by clinicians themselves, too often politicians and bureaucrats seek to effect change by decree, when in reality, clinical practice is shaped by the social and behavioural aspects of HCPs (Berg, 1999). The collective values and behaviours of the individuals which make up a complex system comprise the culture of the system. Supporting the natural processes by which these individuals interact and cooperate, rather than constantly trying to reorganise them, is the key to changing the culture of the system.

Activities relating to PV can be considered a natural hub in the network of healthcare practices; which, pervasively[3] influences the practices and attitudes of HCPs who regard the work as being

[1] Ethnographic research is a qualitative method where researchers observe and/or interact with a study's participants in their real-life environment.

[2] In situ is a Latin phrase that translates literally to "on site" or "in position".

[3] (especially of an unwelcome influence or physical effect) spreading widely throughout an area or a group of people.

out of their scope of responsibilities. This negative association by a few opinion leaders in the network can have a disproportional influence on the attitudes of other colleagues with regard to patient safety.

6.3.1 Failures in sociotechnical systems:

Large complex systems fail not because of technical inadequacy, but rather because they do not recognise the social and organisational complexity of the environment in which they are implemented (Whitney & Daniels, 2013). Baxter & Sommerville (2011) describe common reasons behind the failure of sociotechnical systems including inconsistent terminology, levels of abstraction, conflicting value systems, lack of agreed success criteria, and multidisciplinary work environments.

Changing contexts-of-use, means that the judgement on what constitutes a failure changes, as the effectiveness of the system in supporting work changes. Different stakeholders will interpret the same behaviour in different ways because of different interpretations of 'the problem'. Therefore, the successful operation of a system for one set of stakeholders will inevitably mean 'failure' for another set of stakeholders. This results in a conflict inevitability, as it can become increasingly difficult to establish a set of requirements where stakeholder conflicts are all resolved. As is the case with SRSs belonging to the various role-players in the global PV landscape, these conflicts are represented by the different perspectives and goals of the various SRSs, as discussed in Section 1.2. Another contributing factor to the conflict inevitability is that groups of stakeholders in organisations are often in perennial[1] conflict (e.g. managers and clinicians in a hospital).

Decision-making within a system depends on the power held at some time by a stakeholder group (Markard *et al.*, 2016). Examples of this decision-making power in the PV context includes the setting of regulations by RAs, as well as the design and development of HITs to support SRS interoperability by system developers. There exists a plethora of intricate power relations within a sociotechnical system due to the large number of stakeholders and the overlapping nature of system boundaries.

6.3.2 Challenges in PV related to failures of sociotechnical systems

Healthcare outcomes are produced through the collaborative interactions between people, equipment, tools, documents, and organisational routines (Berg, 1999). Managers and HCPs too often blame the failure of newly implemented technologies on the technical properties (Miller & Sim, 2017; Poon *et al.*, 2017). While technical flaws can certainly result in many

[1] lasting or existing for a long or apparently infinite time; enduring or continually recurring.

problems, it is often the sociotechnical interactions between the new HIT and the existing social and technical systems that lead to undesirable outcomes of HIT implementation. A common misconception is that computerisation inherently improves reliability, but what is often overlooked are the contributions of HCPs clinical judgement, communication within small work groups, and teamwork to patient safety (Baker *et al.*, 2006).

The most common reasons behind system failure in medical informatics are not attributed to hardware or software problems; but rather that systems are built upon incorrect assumptions (Hyysalo *et al.*, 2003), or that they incorporate inaccurate characterisation of medical work, or failure to see the implementation process as an organisational change process (Van der Meijden *et al.*, 2003). The organisational change process associated with STSs is further discussed in Section 6.5.1.

The chances of system failure can be significantly reduced if, throughout the system development, evaluation studies are performed. By making use of qualitative research methods to gain an understanding of user experiences, complaints and change in working relations; organisational learning can be increased, facilitating the organisational change process (Kaplan, 1997).

The failures associated with STSs have been discussed in Sections 6.2.2 and 6.3.1. Rather than aiming to design a perfect system, the design process must be flexible enough, to allow for small errors to be addressed through incremental improvements. By taking the sociotechnical system perspective and using the higher levels of the sociotechnical stack to identify and trap failures, adverse consequences become limited. The goal should be to contain failures within technical systems and not allow the failure to propagate across the sociotechnical system, resulting in failure.

6.4 The problem with standardisation in sociotechnical systems

When considering the process of standardisation in sociotechnical systems it is crucial to understand the balance between system adaptability to local work practices on a low level of abstraction against the interoperability of the system on a higher level of abstraction (Harrison *et al.*, 2007).

Different countries have, for multiple reasons such as economic or cultural, different approaches to work organisation. This is why traditional systems development methods have not been fruitful in providing a global solution to the management of healthcare information. Countries and, in the context of SRSs, organisations, typically adapt these methods to suit their particular needs (Baxter & Sommerville, 2011), as described in the problem statement in Section 1.2.

It would however, be nonsensical to ignore those elements of the system which lend themselves to standardisation. The primary care processes which are employed by HCPs are not necessarily suitable for standardisation because every patient requires a unique combination of care approaches. The extent to which the standardisation of these elements is value adding, is an important consideration, and will result in a system which can alleviate the HCP of some of their duties and ease their cognitive load, thus allowing them to perform the primary care processes more efficiently.

6.5 Organisational change in sociotechnical systems

The implementation of new technology in an organisation is in essence a process of organisational change. For this process to be successful a number of criteria must be met, including a high level of commitment and focus from the users as well as the management of the organisation.

There is a definite need to transition away from the static pre- and post-implementation impacts or notions of discrete change which currently dominate studies in healthcare (Hendy *et al.*, 2005, 2007). Previous attempts to change healthcare practices involving education, persuasion and mandating through hierarchical structure have largely failed due to strong opposing forces such as clinical autonomy and an inability to overcome individual and regional variations in practice. In the case of PV, systems designers should embrace the natural properties of complex systems and empower, engage, and support HCPs in their efforts to promote better and safer patient care. By involving HCPs in the development of HITs which support their work function as well as improve SRS interoperability, organisational learning[1] is increased.

6.5.1 STS transition theory and the reconfiguration pathway

Geels & Schot (2007) are thought leaders in the field of sociotechnical transition pathways. They developed a typology of four sociotechnical transition pathways: (i) *transformation*; (ii) *reconfiguration*; (iii) *technological substitution*; and (iv) *de-alignment and re-alignment*. The four transition pathways clarify the relationship between three structural levels (the multi-level perspective (MLP)) and the role of agency[2]. The MLP is made up of the 'landscape level', the 'regime level', and the 'niche level', which can be seen on the left side of Figure 6.3, along the y-axis.

[1] Organisational learning is the process of creating, retaining, and transferring knowledge within an organisation.

[2] In social science, agency is the capacity of individuals to act independently and to make their own free choices. By contrast, structure is those factors of influence (such as social class, religion, gender, ethnicity, ability, customs, etc.) that determine or limit an agent and his or her decisions (Barker, 2003).

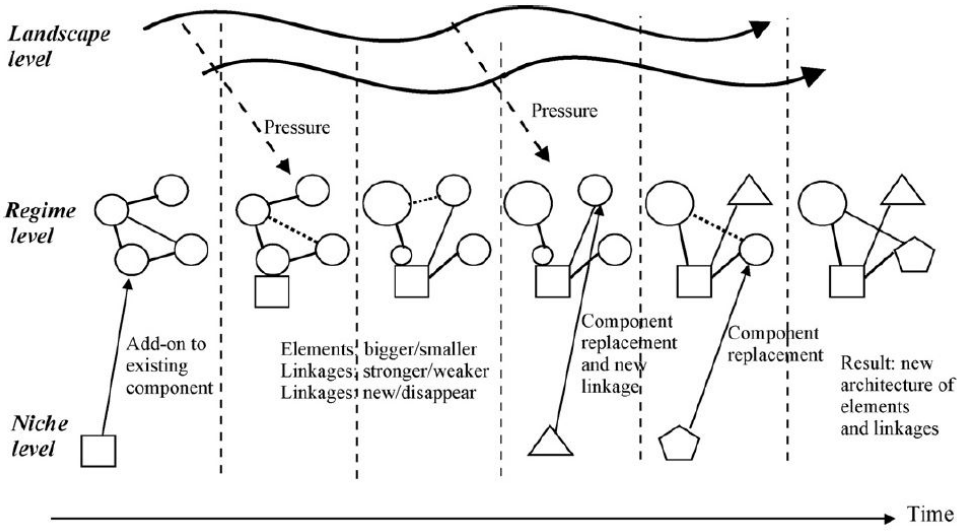

Figure 6.3: Reconfiguration pathway. Geels & Schot (2007).

The *reconfiguration pathway* seen in Figure 6.3 has been identified as the most appropriate of the four pathways to aid in the understanding of the sociotechnical transition that is brought about through the design and implementation of HITs in the context of PV. The landscape level exerts pressure onto the regime level in an exogenous[1] manner, here the regime level is the PV system within a health system. There are political, regulatory, technological, and social forces which are external to the inner-workings of the PV system that create pressure at the regime level. In addition to pressure from the landscape level, the niche level is the micro-level where new technological innovations emerge. These niche-level innovations, whether technological or social, accumulate and can destabilise the system, resulting in the origination of a sociotechnical transition. It is important to understand that these change process are influenced by complex interactions between various system components, and across all levels of the sociotechnical system (Geels & Schot, 2007).

Sociotechnical transitions invariably result in a shift in work roles and responsibilities. More often than not, the shift in work tasks is from those who inherited extra work tasks, from people who considered themselves to be in a position of power in the organisational hierarchy, back to the appropriate people. For example, GPs often delegate the administrative duties of their work practices to the nurses, when in fact, the responsibility to perform those administrative duties is that of the GPs themselves.

[1] Having an external cause or origin.

6.5.2 Capacity building to guide the process of change in sociotechnical systems

According to the work of Berg (1999), HIT interventions that embed pre-fixed sequences of steps in a care process, or that only allow for certain modes of data input would perish amidst the contingencies and pragmatic needs that characterise healthcare work. New competencies for healthcare workers must be established so that higher levels of complexity in work tasks can be established. In other words, the doctors of the future will need to be trained to use emerging technologies whilst understanding the sociotechnical dynamics which undermine their work. Additionally, new HIT initiatives must be developed according to sociotechnical systems design methods. Further theory which supports the study of change and transitions in STSs, is that of Potter & Brough (2004). An adaptation of Potter & Brough's (2004) capacity building pyramid can be seen in Figure 6.4.

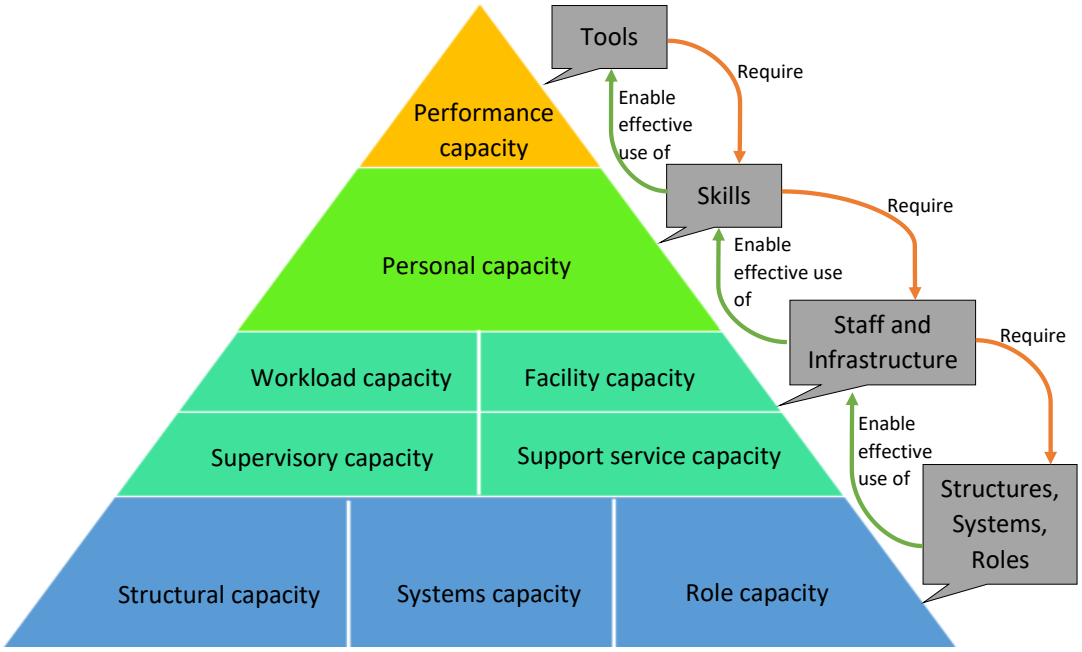

Figure 6.4: Capacity building pyramid. Adapted from (Potter & Brough, 2004).

In developing these new competencies the adapted capacity building pyramid in Figure 6.4, must be considered. Tools and skills are more technical and are easier to change over shorter periods of time, when compared to staff and infrastructure; and structures, systems, and roles; this is partly attributed to the fact that these elements of the system lend themselves to the process of standardisation. Performance capacity is, to a large extent, governed by the tools which HCPs are afforded to make use of. These tools in the context of PV can be understood as being the hardware and software elements of the system. Personal capacity is governed by

the skills that the HCPs are equipped with. The bottom two levels of the capacity pyramid are more socio-cultural and are more resistant to change, requiring more effort and more time to change.

When designing, developing, and implementing HITs, to support HCPs work processes and SRS interoperability; the adapted capacity building pyramid shows how the higher levels of the pyramid require the appropriate capacity in the lower levels, in order to be most effective.

6.6 Chapter 5: Conclusion

Chapter 6 involved discussion on the notion of sociotechnical systems. The activities relating to PV were organised into levels according to the four level health system model. The PV system was described as a sociotechnical system to gain an improved understanding of how best to design and implement HITs in these complex and adaptive health systems. From the findings presented in this chapter we show that HIT innovations can never be fully achieved with technological advances alone. The research dismisses the notion that problems regarding HIT implementations can be solved simply with more or better HIT. The introduction of HIT in sociotechnical systems inevitably leads to organisational change. This organisational change must be strategically guided, thus presenting an opportunity for the development of a maturity model, which is the focus of Chapter 7.

Chapter 7

Development of the Pharmacovigilance Reporting Capability Maturity Model

This chapter deals with the development of a model, based on the concept of a CMM, which can be used by RAs, or similar entities which might own or operate a SRS, to measure, assess, and improve their PV capabilities in terms of various domains and dimensions so as to guide them towards reaching ICH E2B(R3) compliance. The ultimate aim being to contribute towards improving the interoperability of SRSs on a global scale, while also optimally leveraging the value that can be derived from the services offered by *the* UMC.

7.1 Introduction

The development of the Pharmacovigilance Reporting Capability Maturity Model (PVR-CMM) builds on the literature reviews that have been presented in the preceding chapters. Before presenting the development of the PVR-CMM, the most salient inputs to the development of the model are briefly summarised.

The first step towards developing the PVR-CMM is to gain an understanding of the global PV landscape, what is meant by an interoperable spontaneous reporting system, the challenges and barriers which affect the spontaneous reporting of ADRs, and the effects of the lack of an interoperable global PV reporting system, as outlined in Chapter 3. From this, the extent to which interoperability could alleviate these PV challenges was established.

Chapter 4 involved characterising the global PV system by identifying the role players, their responsibilities, and the communication channels between them. This stage of the research also identifies and elaborates on best practices for the reporting of ADRs (the ICH E2B(R3)

standard for electronic ICSR transmission) as well as the solutions and services offered by *the* UMC. By understanding the roles and responsibilities of the various role players, the PVR-CMM is developed with the three perspectives described in Section 7.3 in mind.

The use of maturity models as assessment and improvement guidance tools is investigated in the following step in the research. One application of MMs, as demonstrated in Chapter 5, is to provide guidance towards interoperability. By comparing various MMs and maturity assessment frameworks in an eHealth context, it has been determined that MMs can also feasibly be used for this purpose within the PV landscape.

Taking into consideration the difficulty associated with implementing standardised HITs into large, complex systems, the notion of STSs is investigated in Chapter 6. The PV system was described as an STS to gain an improved understanding of how best to design and implement HITs in these complex systems. Through the conceptualisation of the PV system as an STS, the PVR-CMM development process is more cognisant of social, cultural, and political factors, rather than focusing solely on the technological factors.

7.2 Maturity model development strategy

Becker *et al.* (2009) put forward a procedural model to facilitate the development of MMs; the procedure consists of eight phases. This procedure has been adapted for the purpose of this study. A comparison of Becker *et al.*'s (2009) procedural model and the phases of development of the PVR-CMM can be found in Table 7.1. The phases of the PVR-CMM development have been aligned with the eight phases of Becker *et al.*'s (2009) procedural model. It is important to note that phase 5 has been added to the PVR-CMM development, covered in Chapter 8, while phases 6 through 8 are covered in Chapter 9. The reason for this uncoupling is to allow for Chapter 7 to focus on the model development, while Chapter 8 focuses on the verification of the model to determine whether or not it is suitable for implementation in a case study (Chapter 9), thus allowing for the validation and overall acceptance or rejection of the PVR-CMM. Further discussion relating to the verification and validation process is found in Section 8.1.

Table 7.1: The PVR-CMM seven phases of development compared to Becker *et al.*'s (2009) eight phase procedural model.

Becker et al.'s 8 phase MM development strategy	**PVR-CMM phases of development**	**Chapter section**
1. Problem definition	1. Problem definition	7.3
2. Comparison of existing maturity models	2. Determination of design requirements	7.4
3. Determination of development strategy	3. Comparison of existing maturity models	7.5
4. Iterative maturity model development	4. Iterative maturity model development	7.6 to 8.7
5. Conception of transfer media	5. Verification	8.1
6. Implementation of transfer media	6. Conception of transfer media	9.2.1
7. Evaluation	7. Implementation and validation	9.3 to 9.5
8. Acceptance/Rejection of maturity model	8. Acceptance/Rejection of maturity model	9.5.2.1

The eight phases are executed in Sections 7.3 to 9.5.2.1. The presentation of the final model and the supporting practical recommendations are found in Chapter 9, in Sections 9.2 and 9.4 respectively.

7.3 Phase 1: Revisiting the problem definition

Chapters 3 and 4 discuss the various challenges associated with the spontaneous reporting of ADRs, as well as how SRSs operate and the best practices associated with spontaneous reporting. Spontaneous reporting of ADRs is the cornerstone of data generation in the post-marketing authorisation phase of PV activities. Figure 7.1 depicts how the ICSR is created via collaboration between the ICSR informer and the ICSR creator, typically the patient and/or consumer and an HCP respectively. The creation of the ICSR is usually performed via an HIT application at the operational level. The ICSR is then sent to the primary receiver, which in most cases is the appropriate RA or NCA, which then transmits the ICSR to the appropriate secondary receiver, such as the MAH, which manufactured the drug, or *the* UMC's VigiBase.

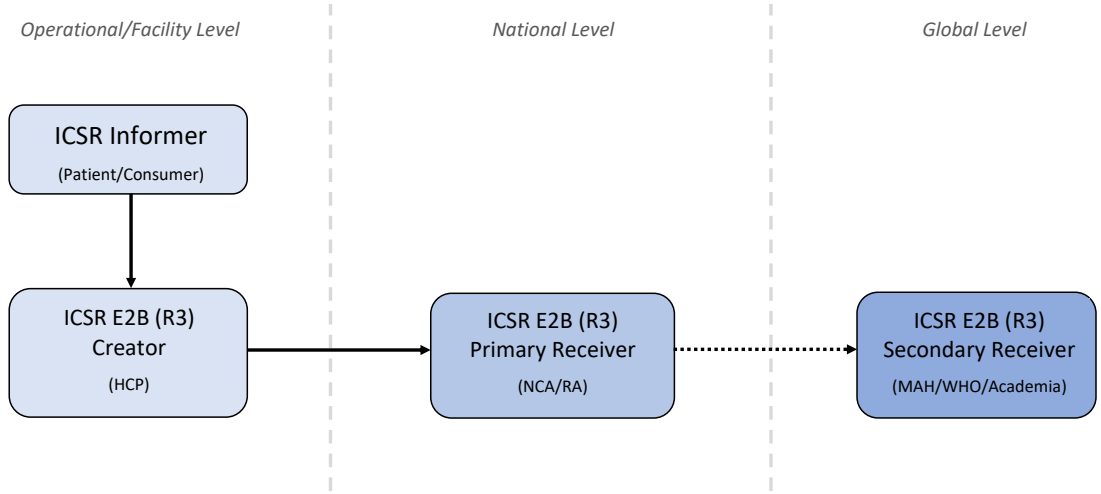

Figure 7.1: ICH E2B(R3) ICSR data flow. Adapted from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (2016).

Figure 7.2 is a conceptual model of a health information system from a patient safety perspective. At the operational level, HCPs interact with HITs in the form of clinical applications which capture patient safety data in multiple forms. Figure 7.2 displays the three stages of data flow on the left hand side (data capture, data storage and aggregation, and data presentation), on the y-axis to the right of the figure, the four levels of the health system are shown, accompanied by the scale of interoperability standards which relate to the three stages of data flow across the various levels of the system.

Data captured via clinical applications, are stored within patient care systems. These patient care systems in combination with data from other sources form the basis of data aggregation for analysis. Population-based analyses can be conducted internally by an organisation such as an RA or healthcare facility, or externally, such as in the case of *the* UMC's Vigi tools and methods. Ultimately, the outcomes of such population-based analyses are disseminated back to the patients, HCPs, or any entity which plays a role in the patient safety system, such as MAHs or RAs.

Standardised solutions in the form of various HIT initiatives are available; it is the failure in adoption and implementation of these solutions that is hindering worldwide PV system interoperability, as discussed in Chapter 6. This failure in adoption and implementation of HITs across the various PV systems hinders efforts to coherently manage PV on a global scale. The primary obstacle to achieving interoperability between SRSs globally is the fundamental difference in purpose of the existing SRSs. This difference in purpose is a result of the differing perspectives of the three main role players at the global level of PV, *the* UMC, the various MAHs, and the RAs representing governments around the world, discussed in Sections 1.2

and 4.7.2. The strength of the global PV system lies in the integration of various national and industry PV systems. While *the* UMC offers substantial support to the WHO member countries, as discussed in Section 4.4, many of the developing member countries lack the capacity and capability to take full advantage of the services offered by *the* UMC.

Maturity models, as discussed in Chapter 5, are primarily used to assess system capabilities and to guide strategically linked continuous improvement processes. Chapter 6 highlights one of the main issues facing HIT designers and implementation teams, i.e. the challenge of bringing together people, policies, and technology. This chapter therefore deals with the development of a model, based on the concept of a CMM, which can be used by MAHs, RAs, or any entity that owns or operates an SRS to measure and assess their PV capabilities; thereby improving ADR reporting or data generation, which is the cornerstone of all PV systems.

The benefits associated with interoperability in the context of PV are incontrovertible. Interoperability is a solution to the risks associated with health information becoming considered a proprietary asset held within stand-alone information systems (Brailer, 2005). As discussed in Chapter 3, fragmentation of PV systems when it comes to collecting and processing ADR reports, leads to errors, loss of information, duplication, lack of coordination, amongst other problems. In the context of an SRS, the question is whether interoperability will emerge as a result of wide-spread adoption of stand-alone systems; or whether a new system should be designed with interoperability standards at the core. When all the necessary stakeholders in PV are collecting ADR information independently of each other but are legally required to share that information with each other, interoperability should emerge as there are demonstrable benefits in terms of costs and ease of sharing information associated with interoperability (Gottschalk, 2009).

Thus, the specific problem that will be addressed by the developed model is the lack of interoperability among SRSs globally. This will be addressed by developing a maturity model, based on the CMM. The aim of which, will be to promote and improve interoperability by addressing the degree of integration of systems involved, providing guidance on which system components need to be improved, as well as providing a means for measuring interoperability progress across the community of SRSs in the global PV landscape.

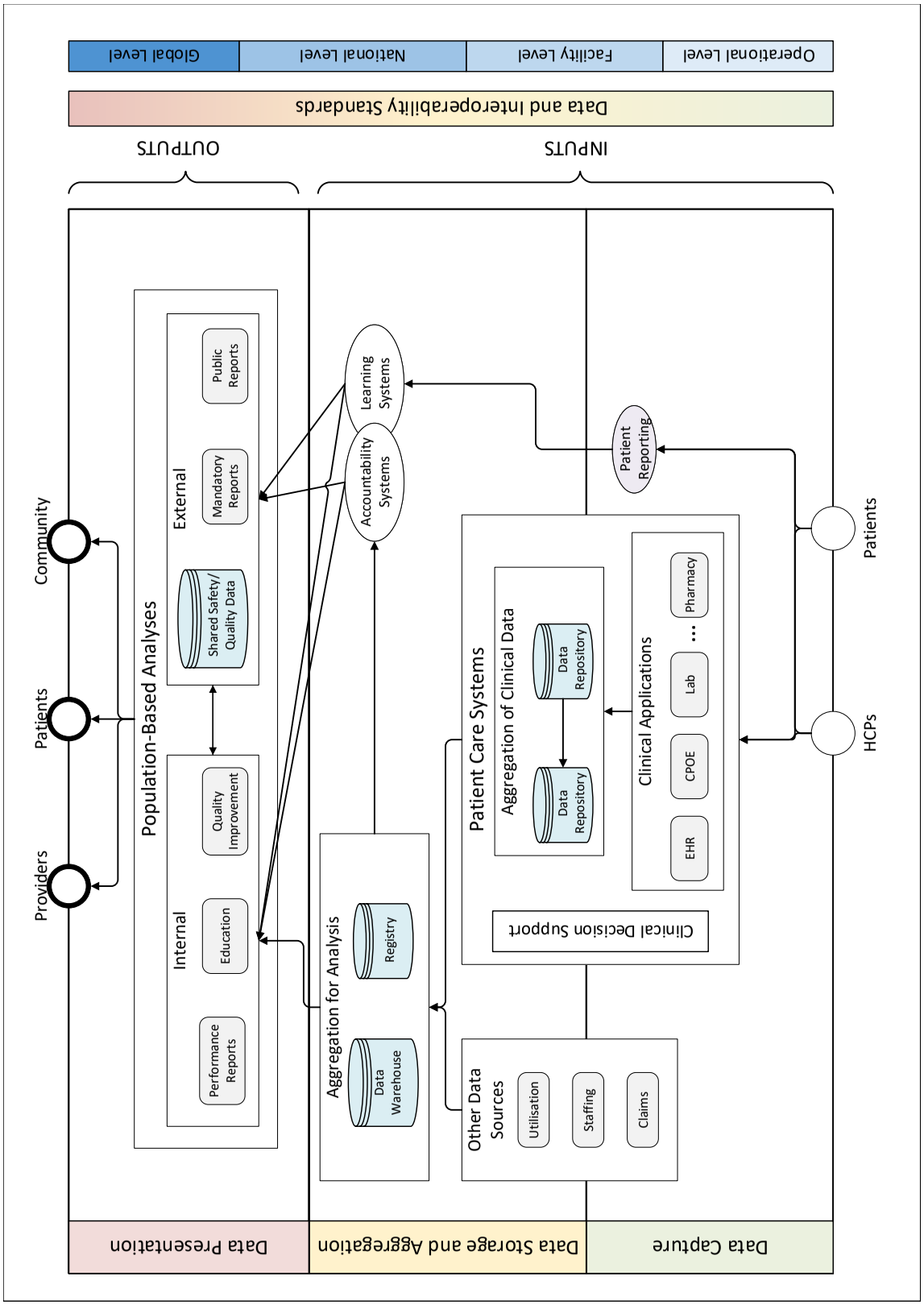

Figure 7.2: A conceptual model of a health information system from a patient safety perspective. Adapted from (Erickson *et al.*, 2003)

7.4 Phase 2: Determination of design requirements

To aid in the development of the PVR-CMM, the necessary design requirements for such a model must be defined. The design requirements are developed from the findings and conclusions of the preceding literature review chapters, as well as with the use of Pöppelbuß & Röglinger's (2011) work on the development of maturity models. Based on a systematic review of a large number of maturity model development strategies, Pöppelbuß & Röglinger (2011) summarise the most pertinent design considerations to adhere to for the design and development of descriptive maturity models. Van Dyk (2013) divide these design considerations into two groups: firstly design considerations in terms of methodology; and secondly, design considerations related to design requirements. This grouping of the design considerations is well suited to this research as a number of the design considerations relating to methodology have already been acknowledged via the use of the MM development procedural model of Becker *et al.* (2009), which was discussed in Section 7.2. The ten basic design considerations of Pöppelbuß & Röglinger (2011), as grouped according to Van Dyk (2013), and the design requirements which are derived from these considerations, are as follows:

Design considerations related to design requirements:

1. Application domain

The first design consideration refers to the application domain of the maturity model that is to be developed. In this case, the maturity model's application domain is the spontaneous reporting of adverse drug reactions in pharmacovigilance. This informs the first design requirement (DR).

> **DR1:** The PVR-CMM can describe all activities relating to the spontaneous reporting of an ADR within PV.

2. Purpose of use

Along with the application domain, the maturity model's purpose of use must be clearly defined. Pöppelbuß & Röglinger (2011) list three types of maturity models, which were discussed in Section 5.4.1. The PVR-CMM will initially act as a descriptive maturity model, used to assess an organisation's spontaneous reporting capability, and then as a prescriptive maturity model in that the model will provide guidance to the organisation on how to increase their maturity across various dimensions. In the case of the PVR-CMM, the purpose of use is described in Section 7.3, and is encapsulated in the following two DRs:

DR2: The PVR-CMM enables the assessment of the maturity of an organisation's spontaneous reporting capabilities.

DR3: The PVR-CMM can be used to guide improvement initiatives.

3. Target audience

The target group refers to the group of people who apply the maturity model, as well as the organisation which they represent, in that the results of the maturity assessment pertain to various other constituents of an organisation (De Bruin *et al.*, 2005). In the case of the PVR-CMM, the target audience is any organisation which owns or operates a spontaneous reporting system for the management of ADR reports. Following discussions with a number of leading global experts in PV, it was decided that the PVR-CMM should be targeted towards regulatory authorities primarily, especially those in developing countries[1]. The PVR-CMM should also be designed in such a way that it can be easily understood by the person or persons who will use it in carrying out a maturity assessment. A well constructed maturity model should seek to emulate a reference model in that it should characterise and structure its components in a comprehensive manner which enables non-specialist users to make sense of, and make use of the model (Organization for the Advancement of Structured Information Standards, 2006).

DR4: The PVR-CMM is designed for the intended use by a specified target audience.

DR5: The PVR-CMM can be used for educational purposes and can be used to explain various aspects of the spontaneous reporting of ADRs to anyone with little to no background in PV.

DR6: The PVR-CMM is presented in an easy to understand manner and can be used by organisations to reach a common understanding of the system and the associated standards.

In the case of DRs 12 and 13, these DRs resulted as a response to subject matter feedback received during verification activities conducted at the later stage of the research. This verification process is described in Section 8.5.

DR12: The PVR-CMM can be used by stakeholders from various disciplines in PV to assess the spontaneous reporting of ADRs at the level in which they are engaged.

[1]These discussion were held at the ISoP-ASoP Mid-Year Symposium & Training Course, held in Nairobi, Kenya, between 6 - 8 May 2019.

4. Class of entities under investigation

Maturity models can refer to various classes of entities. Mettler & Rohner (2009) suggest that typical classes are people, processes, or other objects from a specific application domain. This, together with design considerations 7 and 8, listed below, yield the following two DRs. Design considerations 7 and 8 are discussed further in the section on design considerations relating to methodology.

> **DR7:** The PVR-CMM provides a set of domains, subdomains, and dimensions which characterise all aspects of spontaneous reporting of ADRs in PV.

> **DR8:** The PVR-CMM is designed with sociotechnical systems theory in mind and therefore does not focus solely on the technical components of spontaneous reporting systems.

5. Maturity, maturity levels and maturation paths

The goal, according to De Bruin *et al.* (2005), when developing the capability statements of a maturity model, is to attain a set of statements which are mutually exclusive and collectively exhaustive. Mutual exclusivity is when no two statements are the same; and for the set to be collectively exhaustive, at least of one of the statements must be considered true for each dimension. These principles yield the following three DRs:

> **DR9:** The capability statements of the PVR-CMM are mutually exclusive.

> **DR10:** The capability statements of the PVR-CMM are collectively exhaustive.

> **DR11:** The capability statements and maturity levels accumulate, with each level and statement encompassing the preceding lower levels and statements.

6. Available levels of granularity of maturation

Both, Pöppelbuß & Röglinger (2011) and De Bruin *et al.* (2005), refer to the need for maturity models to be structured in layers according to different levels of granularity of maturation. When a maturity model is structured hierarchically in such a way, it allows for an organisation to make comparisons of maturity levels at a high level of abstraction, such as a domain level; or, to compare maturity at a lower level of abstraction, allowing for more specific improvement areas to be identified, such as within a dimension level. These various levels of granularity allow for the communication of information which may better suit stakeholders which are external to the organisation, for example shareholders and executive bodies; or internal stakeholders such

as different departments or functional units. As stated previously, DRs 12 and 13 were added as a response to subject matter feedback received during verification activities conducted at a later stage of the research. This verification process is described in Section 8.5.

> **DR13:** The descriptions of the capability statements clearly relate to and discriminate between maturity levels.

Design considerations related to methodology:

The following design considerations from the work of Pöppelbuß & Röglinger (2011) are not explicitly linked to the DRs discussed above, but rather, innately incorporated into the methodology of this dissertation, as well as the design and development strategy of the PVR-CMM in this chapter, as summarised in Table 7.1.

7. Definition of central constructs

Design consideration 7 is addressed in Chapters 3, 4, 5, and 6.

8. Underpinning foundations with respect to evolution and change

Design consideration 8 is also addressed in Chapters 5, and 6.

9. Differentiation from related maturity models

This design consideration forms part of the development strategy as described in Section 7.2, as well as being an integral step in Becker *et al.*'s (2009) procedural model, shown in Table 7.1. 18 maturity assessment frameworks and models, from various application fields, are compared in Section 7.2.

10. Design process and extent of verification and empirical validation

Pöppelbuß & Röglinger (2011) build on the work of Benbasat *et al.* (1984), and King & Kraemer (1984) when addressing the extent of empirical validation of maturity models. As part of the development process it is necessary to document to what extent the maturity model under development has been subjected to verification and validation processes. These verification and validation processes can be performed by means of interviews with subject matter experts, questionnaires, case studies, focus groups, and workshops, in an attempt to improve the maturity model's intended usage and performance.

The development of the PVR-CMM included multiple verification and validation processes. The verification and validation strategy is described in Section 8.1 and executed in both Chapters 8 and 9.

7.5 Phase 3: Comparison of existing maturity models

In keeping with the MM development procedure of Becker *et al.* (2009), the next phase is to make a comparison of existing maturity models and frameworks. This comparison is made in order to ensure that a strong foundation of literature is considered, as well as to ascertain whether or not a model or framework already exists which satisfies the DRs stated in Section 7.4. A body of literature surrounding the interoperability of information systems as well as health information systems specifically was studied. A literature review performed by Carvalho *et al.* (2016) found a wealth of maturity models focussing on healthcare information systems and technologies. From this research, a collection of 18 MMs and frameworks were identified. A comparison of these 18 models and frameworks assisted with the selection and characterization of the 30 dimensions included in the PVR-CMM. The 18 models and frameworks summarised in Table 7.2 are grouped together by their application field. The application fields are: (i) PV; (ii) eHealth; (iii) eHealth/interoperability; (iv) interoperability; and (v) IT infrastructure.

Other models and frameworks which could contribute significantly to the development of the PVR-CMM include Leon *et al.*'s (2012) framework for assessing the health system challenges to scaling up mobile Health (mHealth) in South Africa which proposes four key domains: (i) government stewardship; (ii) organisational/behavioural; (iii) technological; and (iv) financial. Similarly, Tanriverdi & Iacono (1999) suggest that the primary barriers to eHealth innovation diffusion can be categorised as behavioural, technical, economical, and organisational barriers. Sittig & Singh (2010) introduces an 8-dimensional model to assist in understanding the challenges inherent in studying HIT. The model will be built upon for the design, development, implementation, use, and evaluation of HIT within complex adaptive healthcare systems. The 8 interdependent dimensions are as follows: (i) hardware and software; (ii) clinical content; (iii) human computer interface; (iv) people; (v) work-flow and communication; (vi) internal organisational features; (vii) external rules and regulations; and (viii) measurement and monitoring.

Of the four models and frameworks within the application field of PV, none are developed following a well regarded reference model, with only one being based on the concept of a maturity model. The SCOPE best practice guide however, does not include an assessment tool. Of the remaining three models and frameworks, two can be used as assessment tools, namely the WHO Data Collection Tool, and the Indicator Based Pharmacovigilance Assessment Tool. The last of the models and frameworks in the PV application field, is the Pharmacogovernance and Modes of Engagement Tool. This last tool however, is not based on the concept of a maturity model, nor is it used as an assessment tool.

7. DEVELOPMENT OF THE PHARMACOVIGILANCE REPORTING CAPABILITY MATURITY MODEL

Although none of the models or frameworks considered in this study were able to satisfy all of the DRs in Section 7.4, the findings from the literature study, in particular with regard to the four models and frameworks in the application field of PV, yielded valuable insights to guide the development of the PVR-CMM. It is evident that HIT designers and implementation teams are tasked with the challenge of bringing together policies, people, and technology; as well as the stakeholders which personify these domains, policy makers, HCPs, and IT developers. User participation must be at the heart of STS design, with users being an integral part throughout the systems development life cycle. Sensitisation and awareness of stakeholders across the system to the value of a sociotechnical approach is essential; as is constructive engagement in terms of involving a multidisciplinary team of developers, engineers and healthcare practitioners throughout the entire SDLC and integrating STS design approaches into the change management processes in the organisation (Baxter & Sommerville, 2011).

Table 7.2: Summary and comparison of existing maturity models and frameworks used in this study.

Designation	Application Field	Levels	Research Method	Components	Assessment tool	Reference model	Author	Reference
IT Systems for ADR Reporting: Best Practice Guide	PV	3	Survey, Case studies	ADR IT system funtionality: *Collect, Record, Report in E2B, Received ADR data analysis* ADR system maturity level: Basic, Well developed, Advanced	n/a	n/a	SCOPE team of the Agency for Medicinal Products and Medical Devices of Croatia (HALMED)	(SCOPE, 2018)
WHO Data Collection Tool - Module 11: Pharmacovigilance	PV	n/a	n/a	Legal Underpinnings, Directives, Organisation and Structure, Internal Procedures, Huamn and Other Resources, Records and Results, Availability of Information.	Yes	n/a	World Health Organization Technical Cooperation for Essential Drugs and Traditional Medicine	(World Health Organization, 2011)
Pharmacogovernance and Modes of Engagement Model	PV	n/a	Literature review	Policy, Law, Regulation (Governing structures, Norms, Policy Instruments, Practices, Institutional authority), Accountability and Transparency, Participation and Representation, Equity and Inclusiveness (Distribution of resources for PV), Ethics (Policy), Effectiveness and Efficiency (System integration and communication), Responsiveness (Risk communication), Intelligence and Information (e-Reporting technology, Risk communication), Stakeholder communication (Pooled resources, Network mobilisation, Communication network).	n/a	n/a	Kathy Moscou, University of Toronto	Moscou (2016)
Indicator-Based Pharmacovigilance Assessment Tool (IPAT)	PV	n/a	Literature review and Delphi method	Components: (Policy, Law, and Regulation), (Systems, Structures, and Stakeholder Coordination), (Signal Generation and Data Management), (Risk Assessment and Evaluation), (Risk Management and Communication). Indicators: Core/Supplementary, Structural/Process/Outcome	Yes	n/a	Strengthening Pharmaceutical Systems	(United States Agency for International Development, 2009)
Electronic Healthcare Maturity Model (eHMM)	eHealth	7	n/a	Entities, Department, Infrastructure.	n/a	n/a	Quintegra Solutions Limited	(Sharma, 2008)
The Healthcare Analytics Adoption Model (HAAM)	eHealth	9	Observation and Expert opinion	New Data Sources, Complexity, Data Literacy, Data Timeliness.	Yes	EMRAM	Health Catalyst	(Sanders et al., 2013)
Telemedicine Service Maturity Model (TMSMM)	eHealth	5	Literature review, Workshops, Case study	Man, Machine, Material, Method, Money.	Yes	CMM	Liezl van Dyk, Stellenbosch University	(Van Dyk, 2013)
Healthcare Usability Maturity Model	eHealth	5	Literature review, Case study	Elements: Focus on Users, Management, Process and Infrastructure, Resources, Education. Maturity phases: 1 Unrecognised, 2 Preliminary, 3 Implemented, 4 Integrated, 5 Strategic.	Yes	Various Usability Models	Healthcare Information and Management Systems Society	(HIMSS Usability Task Force, 2011)
Framework for sharing of National eHealth Strategies	eHealth	5	Literature review	Governance: Leadership and Governance, Strategy and Value Management. Solutions: IEHI, Healthcare Service Delivery, Healthcare Information and Knowledge, Public Health and Healthcare Management and Administration. Foundations and Enablers: Infrastructure, Standards and Interoperability, IT Process Management, (Legislation, Polic and Compliance), Workforce, Adoption Mechanism, Technological and Innovation Trends. Maturity levels: 1 Initial, 2 Ad-hoc, 3 Defined, 4 Managed, 5 Optimised.	Yes	CMM	Joint Action to Support the eHealth Network (JASEHN)	(European Commission, 2017b)
Refined Health European Interoperability Framework (ReEIF)	eHealth/ Interoperability	n/a	Case studies	Layers of Interoperability: Legal and Regulatory (legal and regulatory constraints), Policy (collaboration agreeements), Care Process (alignment of care processes), Information (defining of coding of information), Applications (integrated healthcare systems), IT Infrastructure (communication protocols). Implementation levels: Strategic, Tactical, Operational. Cross-cutting issues: (Standards and Profiles, Certification), (Security, Privacy, Governance).	n/a	n/a	Joint Action to Support the eHealth Network (JASEHN)	(European Commission, 2017a)
A Maturity Model for Interoperability in eHealth	eHealth/ Interoperability	5	Literature review, Case study	Perspectives: Technical, Procedures, Standardisation. Maturity levels: Level 0 (System as silo), Level 1 (Peer-to-peer), Level 2 (Distributed Organisation-bound/Distributed Inter-organisational), Level 3 (Integrated National/Integrated International), Level 5 (Universal).	n/a	Stages-of-growth models	Lex van Velsen, Telemedicine Cluster Roessingh Research and Development Enschede, the Netherlands	(van Velsen et al., 2016)

Continued on next page

Designation	Application Field	Levels	Research Method	Components	Assessment tool	Reference model	Author	Reference
Health Information Systems Interoperability Maturity Model (HISIMM)	eHealth/ Interoperability	5	Literature review and collaboration with Health Data Collaborative	Domains: Leadership and Governance, Human Resources, Technology. Subdomains Maturity levels: 1 Nascent, 2 Emerging, 3 Established, 4 Institutionalised, 5 Optimised.	Yes	CMM	MEASURE Evaluation and the Health Data Collaborative	(MEASURE Evaluation project, 2017)
National E-Health Transition Authority eHealth Interoperability Framework	eHealth/ Interoperability	5	Literature review	Interoperability perspectives:Organisational, Informational, Technical. Core concepts Patterns	Yes	CMMI	National E-Health Transition Authority of Australia	(National E-Health Transition Authority Ltd, 2012)
Maturity levels for Interoperability in Digital Government	Interoperability	5	Literature review	Constraints: Constitutional/legal, Jurisdictional, Collaborative, Organisational, Informational, Managerial, Cost, Technological, Performance. Maturity levels: Computer interoperability, Process interoperability, Knowledge interoperability, Value interoperability, Goal interoperability.	n/a	Stages-of-growth models	Petter Gottschalk, Norwegian School of Management	(Gottschalk, 2009)
GWAC Interoperability Context-Setting Framework	Interoperability	6	Literature review	Interoperability Categories: Organisational (Economic/Regulatory Policy, Business Objectives, Business Procedures), Informational (Business Context, Semantic Understanding), Technical (Syntactic Interoperability, Network Interoperability, Basic Connectivity). Cross-cutting Issues: Configuration and Evolution, Operation and Performance, Security and Safety. Maturity levels: 0 None, 1 Initial, 2 Managed, 3 Defined, 4 Quanititatively managed, 5 Optimising.	Yes	CMM	The GridWise Architecture Council	(The GridWise Architecture Council, 2011)
IT Infrastructure Maturity Model	IT Infrastructure	5	Literature review	Domains: Infrastructure Management, Knowledge, Infrastructure Provisioning, Service Management, Solution Driver, Ecosystem Relationship, Management Focus, Organisation, Agility, Pricing Scheme, Business Interface, Utilisation, Automation and Process Management. Maturity levels: 1 Basic, 2 Controlled, 3 Standardised, 4 Optimised, 5 Innovative.	Yes	CMM	Ferry Haris, University of Twente	(Haris, 2010)
NHS Infrastructure Maturity Model	IT Infrastructure	5	Literature review	Key Capabilities: Common Applications and Services, Infrastructure Hardware Platforms, Network Devices and Services, IT Security and Information Governance, Infrastructure Patterns and Practices, End User Devices, Infrastructure Governance, Business Alignment, Procurement, People and Skills, Value Management; Principles, Standards, Procedures and Guidelines. Maturity levels: 1 Basic, 2 Controlled, 3 Standardised, 4 Optimised, 5 Innovative.	Yes	CMM	Andy Savvides, NHS Connecting for Health	(Savvides, 2011)
Maturity Model for Hospital Information Systems (HISMM)	IT Infrastructure	6	Literature review and Survey	Maturity Influencing Factors: Data analysis, Strategy, People, Electronic medical record, Information security, Systems and IT Infrastructure.	n/a	Stages-of-growth models	Joaõ Vidal Carvalho	(Carvalho et al., 2018)

7.6 Phases 4 and 5: Iterative maturity model development and verification

Phases 4 and 5 in Becker *et al.*'s (2009) procedural model, shown in Table 7.1, are "Iterative maturity model development" and "verification", respectively. In this section the first generation of the PVR-CMM is developed, thereafter in Chapter 8, the PVR-CMM is subjected to verification processes in order to ascertain which aspects of the maturity model might require improvement, resulting in the second iteration of the PVR-CMM. For the first generation, the domains, subdomains, and dimensions have been selected from the findings of the preceding literature review chapters as well as from existing maturity models which are discussed in Section 7.5. The PVR-CMM is developed in such a way that it aims to be easily understood at a high level, with the details of capability maturity and interoperability maturity of the dimensions being addressed as the user delves deeper into the model. The PVR-CMM is comprised of three domains which include seven subdomains and 30 dimensions. As discussed in Chapter 5, research suggests that interoperability results as a product of standardisation in four domains: technology, syntax[1], semantics[2], and pragmatics[3].

The PVR-CMM is structured with sociotechnical system engineering principles in mind, that is to say, placing equal importance on the social, political and environmental (workplace) factors (Baxter & Sommerville, 2011). The domains are organised accordingly into three categories: Organisational (pragmatic), Informational (syntax and semantic), and Technical. These three domains lend themselves to the discussion of capability maturity as well as interoperability, and are consistent with the findings of the literature review in Table 7.2.

The PVR-CMM further breaks down these three domains and provides subdomains. The subdomains within the organisational domain characterise the pragmatic aspects of interoperability in PV. The informational subdomains characterise the semantics of interoperability, and the technical subdomains emphasise the syntax or format of the information being exchanged between systems. PV systems involve complex interactions between healthcare professionals, computer hardware and software, as well as the physical work environment within which they operate, all the while being exposed to external pressures from ever changing political, technological, cultural and social factors.

[1]Syntax standardisation refers to the agreement on the structure and language of the message exchanged by heterogenous applications across a network.

[2]Semantic standardisation refers to the extension of syntactic standardisation, that is to say the meaning of the messages are mutually understood.

[3]Pragmatic standardisation refers to agreements on protocols and practices which are prompted by specific messages.

The PVR-CMM is developed for a target audience with a presumably good understanding of the concept of interoperability, as well as familiarity with spontaneous reporting systems, and general process improvement concepts such as the PDCA cycle. Users of the PVR-CMM with this level of understanding should be expected to derive value from the PVR-CMM by being able to adapt and refine the model to suit their organisation's individual needs. Ultimately, the PVR-CMM is developed for use by RAs, MAHs, and any other organisation involved in the ownership or operation of an SRS.

7.6.1 PVR-CMM domains and subdomains

The Interoperability Framework by National E-Health Transition Authority Ltd (2012), and the Smart Grid Interoperability Maturity Model prepared by The GridWise Architecture Council (2011) considered interoperability goals from three perspectives, *Organisational*, *Informational*, and *Technical*. The PVR-CMM further breaks down these three domains and provides seven subdomains, shown in Figure 7.3. The subdomains within the organisational domain, coloured blue in Figure 7.3, characterise the pragmatic aspects of interoperability in PV. The informational subdomains, coloured green in Figure 7.3, characterise the semantics of interoperability, and the technical subdomain, coloured yellow in Figure 7.3, emphasise the syntax or format of the information being exchanged between systems, as well as the technical capability of the system.

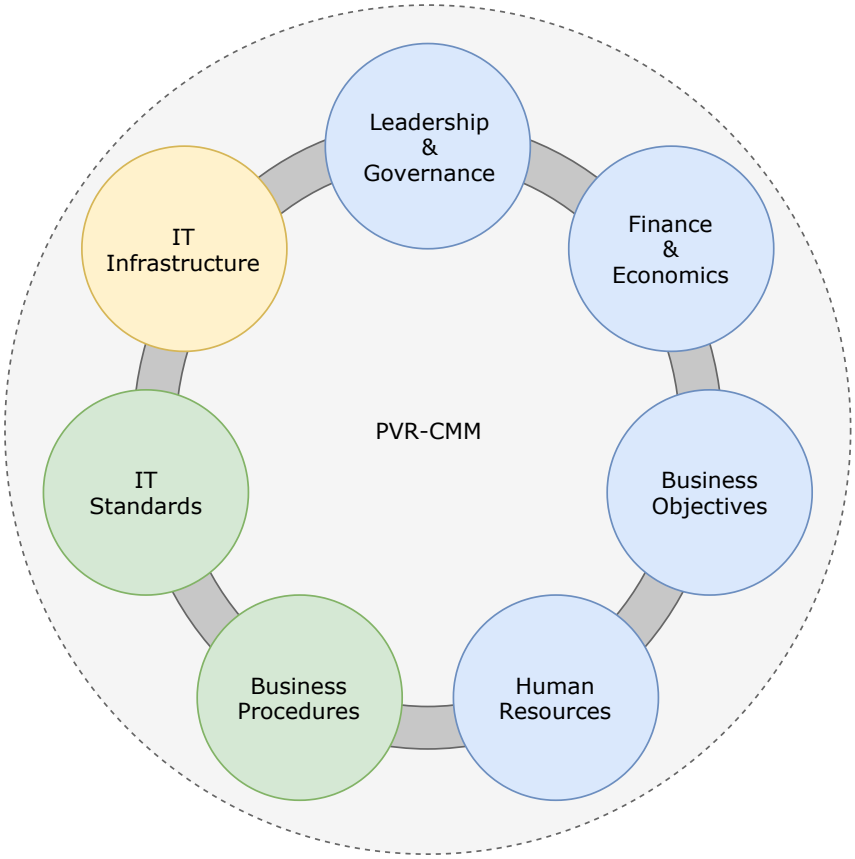

Figure 7.3: The seven subdomains of the PVR-CMM.

7.6.2 PVR-CMM dimensions

The 30 dimensions included in the PVR-CMM will be listed below and motivation for their inclusion in the model will be provided. The contextual definition for each of these dimensions is included in the PVR-CMM itself, in the fourth column.

1. Organisational (Pragmatics)
   (a) Leadership and governance
      i. Law, regulation and policy
         This dimension serves as acknowledgement of the existence of the appropriate legal provisions that mandate and guide all PV related activities. From an interoperability perspective it is necessary to have a common understanding of legislation relating to the exchange of information and the associated security and privacy issues. Legislation and regulatory guidelines must be compatible and define the boundaries of interoperability between two ICT systems.
      ii. Governance structures and commitment

Governance structures are those consisting of the highest executive management of the organisation. The governance structure should enable management to ensure the organisations compliance with the relevant legislation. Governance impacts change management, regulatory compliance, and also directs the progress of evolving policies and procedures towards interoperability.

iii. Business continuity and responsiveness

Certain PV processes are critical and the appropriate business continuity plans should be developed in a risk-based manner. These processes include collection, processing, management, and timely transmission of ICSRs. Back-up systems allowing exchange of critical information within an organisation, between organisations, or between the MAH and the RA.

iv. Data ethics/ownership

Data ethics addresses the moral dimension of data management. This includes ensuring adherence to ethical principles throughout data generation, recording, curation, processing, dissemination, sharing, and use. With the aim of interoperability being the sharing of data, it is important to stipulate the ownership of the data and to protect and uphold the interests of the owner.

v. Monitoring of performance and effectiveness

The organisation should clearly define performance indicators which can be used to continuously monitor the performance of PV activities. Monitoring of performance will include activities such as reviews, audits, compliance monitoring, and inspections. Good PV practices have been defined by the European Medicines Agency and can serve as a set of quality requirements for the various PV activities. Corrective and preventative measures can be implemented as a means of addressing performance shortcomings.

vi. Transparency and accountability

Transparency instils trust and confidence in the organisation and their system by the public. Accountability refers to the organisation taking responsibility for its actions. Both transparency and accountability are exercised in a PV context through the clear communication of post authorisation safety studies (PASSs) and patient safety update reports (PSURs) by the MAH.

vii. Partnerships

Patient safety and PV activities must be considered when forming and managing partnerships. In the case where multiple partner organisations make use of the same PV system, each partner must ensure that the PV system functions to meet their individual regulatory compliance needs.

viii. Stakeholder communication

Provisions for timely and effective communication of patient safety information or safety concerns to the relevant stakeholders (consumers, HCPs, MAH, RAs, etc.), be it within an organisation or between organisations. This also applies to communication between MAHs and their respective RAs. Coordination and cooperation between the various parties involved in communicating patient safety information, as well as the management of communication tools and channels should seek to improve access to information by those in need of the information.

ix. Organisational strategy alignment

It is important that the organisation has a shared understanding of the PV operating model across all levels of the organisation as well as a common understanding of the role of the organisation within the global patient safety system. Different functional units of an organisation, such as manufacturing, sales and marketing, and quality control, may have contradicting goals and incentive structures, which do not focus on patient safety.

x. Building a culture of safety

By developing and maintaining a system of shared actions, values, and beliefs, the safety culture will permeate throughout the organisation. A strong culture of safety can help shape the way in which the organisation views PV, from that of a collection of compliance and risk mitigation activities, to a means of developing a set of standard business procedures which yield a competitive advantage.

xi. Organisational change management

Change management processes need to be established to guide the adoption of newly identified best practices and updated work procedures. Change management is critical when dealing with an ever-changing business environment and the constant introduction of new technologies.

(b) Finance and economics

i. Financial management

A dedicated budget for PV-related activities is crucial. Procedures must be in place to ensure correct spending of funds in the public sector. A proactive approach to investing in innovative technologies must be adopted, e.g. the case of the electronic health record (EHR).

ii. Financial resource mobilisation

Activities relating to the acquisition of new financial resources for the organisation, are vital to guarantee the continued availability of financial resources. These financial resources could include grants, investments from the private sector, or monetary donations from international aid organisations.

(c) Business objectives

i. Regulatory compliance

Organisational policies and processes must always be cognisant of, and remain compliant with, regulatory compliance policies. In order to maintain regulatory compliance, awareness of the applicable legislation and regulations is critical across all stakeholders in the PV system.

ii. Resource efficiency and business sustainability

Business sustainability in this context refers to the organisations ability to continually control the costs and benefits of interoperability while sustaining the overall quality and performance of their spontaneous reporting system. Achieving efficient utilisation of resources is to exploit system inputs to maximise system outputs, while minimising wasted resources.

iii. Data management

Data management refers to the set of procedures and policies which govern the management of data within the SRS. This includes how data are captured, collected, stored, transmitted and processed.

(d) Human resources

i. Human resources policy

This dimension serves as acknowledgement of the existence of the necessary policies which specify roles and responsibilities for PV in the organisation. Every organisation is legally required to designate a qualified person for PV, this person is tasked with overseeing all PV related activities within the organisation.

ii. Human resources capacity

This refers to the availability of personnel with the relevant and required characteristics, attributes, and capabilities to perform the specified PV roles. PV is a responsibility that is shared across functional business units within an organisation and therefore requires personnel across all stages of the system life cycle.

iii. Human resources capacity development

Awareness, education, and training initiatives aimed at the development of a strong PV culture within the organisation. An organised activity with clear

learning outcomes that aims to impart knowledge and skills, shape attitudes, and develop specific competencies and capabilities in personnel.

2. Informational (Syntax and semantics)

   (a) Business procedures

      i. Data capture

      Methods of capturing data associated with suspected ADRs and the technologies involved. The WHO states that an ADR reporting form is one of the minimum requirements for a functioning spontaneous reporting system.

      ii. Data storage and aggregation

      The WHO states that an ADR report database is one of the minimum requirements for a functioning spontaneous reporting system. The methods of aggregating data for statistical analysis, as well as methods for duplicate detection are important when considering the spontaneous reporting system.

      iii. Workflows

      Workflows detail the sequential steps taken when performing business processes and typically involve standard operating procedures (SOPs).

iv. Data presentation/transmission

The format in which the ICSR is transmitted from the sender to the receiver. Currently the best practice is the ICH E2B(R3) standard for the electronic transmission of ICSRs with backwards/forwards compatibility.

(b) IT standards

i. Data standards

To achieve syntactic interoperability the ICT systems which seek to interoperate must make use of specified data formats and communication protocols.

ii. Information content

The data encoded in an ICSR must collectively represent information that is interpreted in the same way by the ICSR sender and receiver.

iii. Data protection, privacy, and security standards

Information shared by consumers and HCPs has associated rights attributed to the consumers and HCPs, these rights must be protected and respected.

iv. Information exchange and interoperability standards

For interoperability to occur, the interacting ICT systems must agree on the use of standard messaging formats.

3. Technical

(a) IT infrastructure

i. ICT hardware

ICT hardware refers to the physical hardware necessary for the effective and efficient operation of a spontaneous reporting system.

ii. Network

The network refers to the existence of the appropriate IT infrastructure to enable the transmission of ICSRs over a local area network (LAN) or a wide area network (WAN).

iii. Development and maintenance

This dimension refers to the development and maintenance of technologies and standards to ensure optimal performance of the spontaneous reporting system. It is important to note that maintenance involves different activities at the local and global levels.

7.6.3 Maturity

The PVR-CMM makes use of two maturity scales, relating to capability maturity and interoperability maturity respectively. It is believed that by providing two scales according to which maturity can be measured, the PVR-CMM user will better understand how the two perspectives interact with each other. The capability levels are defined in the PVR-CMM exactly as those in the original CMM, developed by the CMMI Institute (2018), the CMMI definitions are provided in Table 5.1. As discussed in Chapter 5, the term *capability* is associated with specific business processes or a practice area within an organisation; while *maturity* is described as the degree to which an organisation has explicitly and consistently deployed processes, according to their business objectives. In terms of organisational interoperability, the PVR-CMM was developed using a combination of the levels proposed by Gottschalk (2009) and van Velsen *et al.* (2016), as described in Section 5.6.2. These interoperability maturity levels are summarised in Table 7.3.

Table 7.3: Interoperability maturity levels for the PVR-CMM

Interoperability maturity level	**Description of interoperability maturity level**
Level 1: **System as silo**	Single technology. No standardisation. Technical and semantic issues are solved.
Level 2: **Peer-to-peer**	Two systems linked for simple exchange of data. Work processes are linked.
Level 3: **Distributed** (Organisation bound; Inter-organisational)	Linking of homogenous systems for a common objective. Knowledge is shared.
Level 4: **Integrated** (National; International)	Linking of heterogenous systems for a common goal. Benefits are shared.
Level 5: **Universal**	Systems can connect and disconnect freely and exchange data without serving a common goal.

7.7 The PVR-CMM V1

This chapter has described the activities leading up to the development of the first iteration of the pharmacovigilance reporting capability maturity model (PVR-CMM). Together, the DRs defined in Section 7.4, as well as the model components described in Sections 7.6.1 and 7.6.3, seek to elucidate the model's structure. The high-level structure of the PVR-CMM is depicted

in Figure 7.4 and is justified and motivated in Section 7.6. The first generation PVR-CMM (PVR-CMM V1) is presented in its entirety in Appendix A. With reference to the high-level structure of the PVR-CMM in Figure 7.4, the first three columns from the left indicate the groupings of the dimensions into their respective domains and subdomains. Beginning with the organisational domain, the 30 dimensions are listed according to their subdomains, along with their contextual definitions. Moving from left to right, the capability maturity statements and the interoperability maturity statements are provided in pairs, according to their level of maturity, starting at 'level 1' and moving to 'level 5'.

Domain	Subdomain	Dimension	Contextual definition	Level 0	Level 1 Capability maturity	Level 1 Interoperability maturity	. . .	Level 5 Capability maturity	Level 5 Interoperability maturity
Organisational (pragmatics)	Leadership and governance	Dimension 1 Law, regulation and policy	Dimension 1 Definition		Dimension 1 Level 1 Capability statement	Dimension 1 Level 1 Interoperability statement	. . .	Dimension 1 Level 5 Capability statement	Dimension 1 Level 5 Interoperability statement
	Finance and economics	.	.	.	.	.	. . .	.	.
	Business objectives	.	.	.	.	.	. . .	.	.
	Human resources	.	.	.	.	.	. . .	.	.
Informational (Syntax and semantic)	Business procedures								
	IT standards								
Technical	IT infrastructure	Dimension 30 Development and maintenance	Dimension 30 Definition		Dimension 30 Level 1 Capability statement	Dimension 30 Level 1 Interoperability statement	. . .	Dimension 30 Level 5 Capability statement	Dimension 30 Level 5 Interoperability statement

Figure 7.4: The high-level structure of the PVR-CMM.

7.8 Chapter 6: Conclusion

This chapter focussed on the development of the PVR-CMM V1. The problem statement was revisited and the target audience for the PVR-CMM was specified. The design requirements for the PVR-CMM were listed and a comparison was drawn between 18 models and frameworks from a variety of application fields within a healthcare context. The findings of this comparison assisted with the selection and determination of the PVR-CMM structure in terms of domains, subdomains, and dimensions. The three domains, seven subdomains, and 30 dimensions were listed and a motivation for their inclusion was provided. The two maturity scales, capability maturity, and interoperability maturity were discussed and motivated. The chapter concludes with a description of the first generation of the PVR-CMM, namely the PVR-CMM V1, as well as a graphical representation of the model's high-level structure. Following the development and population of the model, Chapter 8 will address the verification of the model's constructs and content, thereafter allowing for incremental improvements to be made.

Chapter 8

Verification and model refinement

In this chapter the PVR-CMM V1 is subjected to verification in order to determine the model's relevance and the veracity of it's constitution. The subtle, yet significant difference between verification and validation is discussed; thereafter, the verification and validation strategy of the PVR-CMM is detailed. The tools and methods involved in this strategy are described, as well as the outcomes and results yielded through the application of these tools and methods. A deviation to the verification strategy is discussed and executed, resulting in more well founded verification outcomes.

8.1 Introduction

Following the development of the PVR-CMM V1, the constructs and contents of the model must be tested for relevance and rigour (De Bruin *et al.*, 2005). The verification phase of the PVR-CMM development is completed in the remainder of this chapter, followed by the incremental improvement or refinement of the model based on the outcomes and feedback received from the verification activities. The final version of the PVR-CMM is presented in Section 9.2.

The fourth and seventh phases of Becker *et al.*'s (2009) procedural model are "iterative maturity model development" and "evaluation", respectively. In the PVR-CMM phases of development, shown alongside Becker *et al.*'s procedural model in Table 7.1, there is an additional "verification" phase. This is because the verification process will inform the model refinement, thereby making up the iterative nature of the PVR-CMM development. Here, it is important to distinguish between *verification* and *validation*.

Some of the feedback received from SMEs in this chapter, was incorporated into the development of the design requirements, which have already been presented in the previous chapter, in Section 7.4.

8.2 Verification versus validation

In general, verification is concerned with the design and methods employed in research, whereas validation is concerned with measuring the outcome of the research. For the purpose of this research, the validation of the PVR-CMM can only be executed once the model has been subject to the necessary verification processes. Verification and validation are two separate procedural actions, that together, can be used to ascertain whether or not a product or system meets the required standards and specifications. In the literature surrounding maturity model development and testing, the two terms, along with the concepts of *internal* and *external* validation are often used interchangeably. For the purpose of this research, these terms and concepts will be defined here. The IEEE Standards Coordinating Committee's (1990) definitions of verification and validation are deliberately contrasting, so as to remove any uncertainty when using the terms.

Verification is defined as:

> "The process of evaluating a system or component to determine whether the products of a given development phase satisfy the conditions imposed at the start of that phase." (IEEE Standards Coordinating Committee, 1990)

Whereas, **validation** is defined as:

> "The process of evaluating a system or component during or at the end of the development process to determine whether it satisfies specified requirements." (IEEE Standards Coordinating Committee, 1990)

Validity is concerned with the integrity of the conclusions that are generated from a piece of research and is often considered an important criterion of research (Bryman & Bell, 2015). The validation of the PVR-CMM V2, the iteration of the PVR-CMM which is the product of the verification and refinement process, will be conducted in Chapter 9.

8.3 Verification and validation strategy

In the case of this research, the aim of the verification process is to engage with subject matter experts (SMEs) from a diversity of backgrounds, such as those in regulatory capacities, as well as in the pharmaceutical industry, in order to determine the accuracy, applicability, integrity, and value of the PVR-CMM and it's development in this study.

Following the initial verification of the PVR-CMM, discussed in Section 8.5, the author recognised a potential limitation in the verification activities leading up to that point. The initial

verification, although valuable and encouraging, engaged only SMEs from pharmaceutical organisations, thereby failing to obtain inputs from SMEs that are experienced in a regulatory capacity. To address this, a second round of verification activities was executed. This time engaging with a more diverse (in terms of their role in the pharmaceutical industry), yet more focussed (in terms of their involvement in SRSs and their knowledge thereof) cohort of subject matter experts. This deviation in the verification strategy is described in Section 8.5.5 and the remainder of this chapter, thereafter. Figure 8.1 shows the strength of the verification and validation strategy in this study. With the addition of subject matter expert input, as well as the provision of the SME's industry (or regulatory) perspectives, the development of the PVR-CMM V2 benefits from the research method known as triangulation. Triangulation is described in the research methodology section in Chapter 1.

The final methodological design consideration stated in Section 7.4 is the extent of empirical validation. For the purpose of this research, and in the search for true objectivity, the PVR-CMM must be subjected to validation by an entity which is not involved in the development and verification activities. De Bruin *et al.* (2005) state that the issue of generalisability of maturity models can only be addressed if the maturity model in question is deployed to an entity that is external to the the development and verification of the maturity model. For this reason, the PVR-CMM must be tested in a real-world setting, with an organisation that has not been involved in the model's development or verification.

8.3.1 Verification criteria

For the PVR-CMM verification processes described in Sections 8.5 and 8.6, the subject matter experts are provided with questions which collectively seek to determine whether or not the PVR-CMM holds up to the criteria, developed by Van Dyk (2013):

- The PVR-CMM is **clear**: it is easily understood and implemented,
- The PVR-CMM is **useful**: it reflects the important dimensions of the management of an SRS,
- The PVR-CMM is **reliable**: it allows for continuous assessment over time by different stakeholders,
- The PVR-CMM is **valid**: it is a true measure of what it purports to measure, and,
- The PVR-CMM is **practical**: it can be implemented in a timely manner, to inform the continuous improvement processes and guide decision-making.

The specific questions and verification methods are described in detail in Sections 8.5 and 8.6.

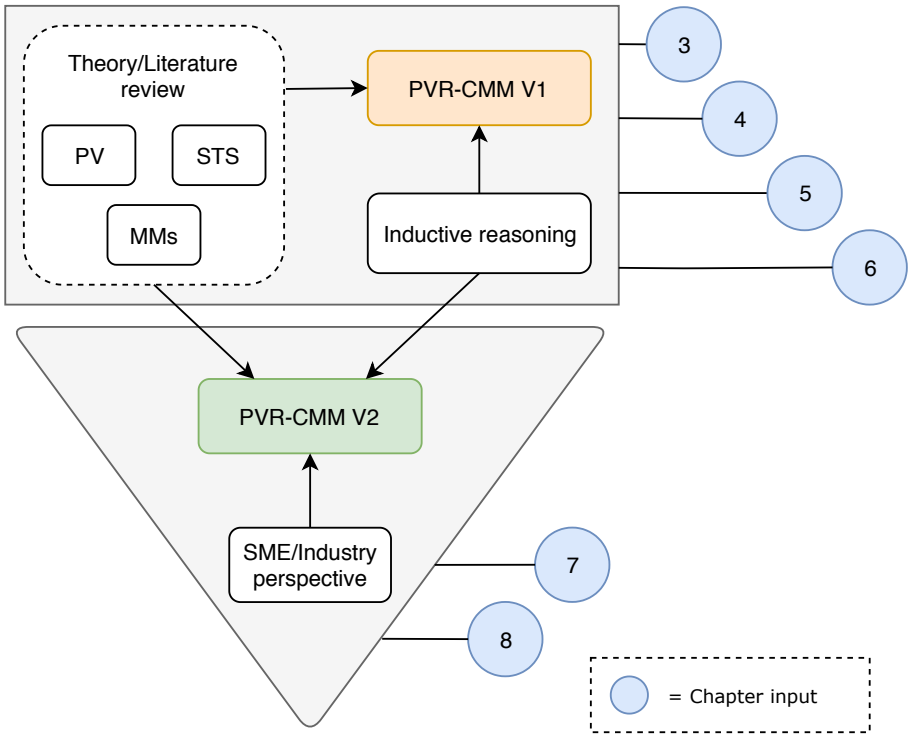

Figure 8.1: The use of triangulation in this study to improve the development of the PVR-CMM, resulting in the PVR-CMM V2.

8.4 Verification and validation instruments and methods

An *instrument*, in the context of verification and validation testing, is a measurement device which a researcher can make use of to engage with research participants, to acquire feedback and answers to specific questions pertaining to their research topic. When selecting an instrument such as this, one must consider the type of feedback that is being sought, as well as the applicability and usability of the instrument. Here, the usability of the instrument is defined as being the ease with which the researcher can administer it, the ease with which the instrument can be interpreted by the participant, as well as how easily the resultant information can be interpreted by the researcher. The self-completion questionnaire, the instrument of choice in this research, makes use of a five point Likert scale[1] consisting of a symmetric agree-disagree scale which the respondents could select to represent their attitude towards a series of questions.

8.4.1 Questionnaire respondents

A number of SMEs were contacted and asked to assist with the verification of the PVR-CMM via the self-completion questionnaires. For the purpose of this research, a number of

[1] A scale used to represent people's attitudes to a topic.

factors were considered when identifying SMEs. These factors include: (i) the role of the SME within their organisation, their occupation, or the relevance of their experience; (ii) academic qualifications; (iii) the depth of their experience, or number of years in the pharmaceutical industry; and (iv) the SME's affiliation (MAH/regulatory/academia etc.) and geographical region. Table 8.1 summarises the characterisation of the 14 SMEs who participated in this research.

This list of SMEs was expanded to include the addition of SMEs number 5 through 14, who were identified in response to the concerns raised in Section 8.5.5.

Table 8.1: Characterisation of the SMEs who were involved in the verification and validation of the PVR-CMM.

SME no.	Role	Affiliation	Education	Relevant experience (years)
1	Qualified person for pharmacovigilance.	Pharmaceutical company, Oss, Netherlands.	Diploma.	20
2	Senior manager, Application development and support, central safety department.	Multinational pharmaceutical company (A), Wavre, Belgium.	BSc, MSc.	20
3	Medical advisor.	Multinational pharmaceutical company (A), Johannesburg, South Africa.	MBChB, PGDip(Pharm).	5
4	Independent consultant.	Independent, Nairobi, Kenya.	MBChB, MSc.	4
5	Principal pharmacovigilance pharmacist.	Ministry of Health, Swaziland.	BSc (Hons), PGDip (Pharm), MSc, PhD.	13
6	Regulatory officer: Pharmacovigilance.	Uganda National Drug Authority.	BPharm.	5
7	Pharmacovigilance country head.	Multinational pharmaceutical company (B), Nairobi, Kenya.	BPharm, MPharm, MBChB.	6
8	Senior programme officer.	African Union Development Agency (AUDA-NEPAD) NEPAD Agency.	BPharm.	18
9	DPhil (PhD) candidate.	University of Oxford.	BPharm, MPharm.	1
10	Acting director[1], Board member[2,3].	[1]WHO African Collaborating Centre for Pharmacovigilance, [2]Ghana Ministry of Health, [3]International Society of Pharmacovigilance.	BSc, MSc, PhD.	10
11	PhD candidate.	University of Sheffield.	BSc, MPharm.	3,5
12	Principal consultant[1], Board member[2].	[1]NDA Regulatory Science, [2]International Society of Pharmacovigilance.	MBChB.	25
13	Head of pharmacovigilance global policy strategy[1], Board member[2].	[1]Multinational pharmaceutical company (B), [2]International Society of Pharmacovigilance.	MBChB, PhD.	28
14	Founding member[1], Board member[2], Expert advisor[3].	[1]Uppsala Monitoring Centre, [2]International Society of Pharmacovigilance, [3]World Health Organisation.	BSc, MSc, PhD.	41

8.5 First verification of the PVR-CMM V1

Verification can be measured in many ways. For the purpose of this research, a number of SMEs were requested to verify that the PVR-CMM stood up to predetermined verification

criteria that addressed the face validity and construct validity of the PVR-CMM (Bryman & Bell, 2015). This was achieved by providing each subject matter expert with a brief summary of the research methodology leading up to the development of the PVR-CMM, a copy of the PVR-CMM itself, as well as a self-completion questionnaire. For the first verification of the PVR-CMM V1, SMEs one to four[1] were engaged.

8.5.1 Verification questions: First verification

Together with the self-completion questionnaire, which can be found in Appendix B.2, the SMEs received a 'pre-reading document' which summarised the relevant literature findings and development process of the PVR-CMM. The pre-reading document can be found in Appendix B.1. The detailed responses to the self-completion questionnaires can be found in Appendix B.3. For ethical reasons and to protect the privacy of the SMEs and ensure confidentiality of their responses, the personal information has been redacted from this dissertation.

The questions, shown in Table 8.2, were designed to test the overall construct validity of the PVR-CMM, and to assess whether or not the design objectives have been achieved. De Bruin *et al.* (2005) state that construct validity is made up of face validity and content validity. In order to test that the theoretical basis upon which the model has been developed is sound, these two measures of validity must be determined, before the maturity model may be considered ready for implementation. Face validity is a measure of how well the DRs have been translated and achieved in the model and content validity is a measure of the extent to which the literature review covered the subject area, as well as the breadth of the literature review.

The self-completion questionnaire consists of 19 questions. The first five questions address details pertaining to the SME/respondent, specifically to their relevant experience. To test for content validity, the SMEs were asked a high level question relating to the research methodology (limited to the development of the PVR-CMM only), represented by question 2.1, as well as two questions to determine whether two of the literature review findings are valid, represented by questions 3.1 and 3.2. To test for face validity, the SMEs were asked to what extent they

[1]SME number one is employed as a pharmacovigilance officer, with a diploma in pharmaceutical management and has been working in the pharmaceutical industry for 20 years. SME number two has 20 years of experience and is the senior manager of application development and support, for the 'Global Pharmacovigilance Information Management Services (GPVIMS)' of a top ten ranked independent multinational pharmaceutical and biotechnology company (ranked by revenue). SME number two was a faculty member for the 'EMA EudraVigilance Information Day' in June 2017, which focussed on the ICH E2B (R3) Implementation Working Group. SME number three has five years of experience and is a medical advisor for a multinational pharmaceutical company, holding a medical degree as well as a postgraduate diploma in pharmaceutical science. SME number four is a medical doctor with a masters degree in public health, and has four years of experience in the pharmaceutical industry, having previously worked for a large multinational pharmaceutical and biotechnology company.

agreed that the PVR-CMM met the DRs defined in Chapter 7, these questions are numbered 4.1 through 4.11.

8.5.2 Subject matter expert feedback: First verification

From the 14 questions relating to the research methodology, the literature review findings, and the PVR-CMM, a maximum possible score of 70 per SME, or 20 per question, can be achieved using a 5 point Likert scale[1]. Table 8.2 summarises the results of the self-completion questionnaire and highlights any questions to which the respondents might have selected 'unsure', 'disagree', or 'strongly disagree', corresponding with values of 3, 2, and 1, respectively. The questions to which the SMEs responded with 'strongly disagree', 'disagree', or 'unsure', are discussed in Section 8.5.3.

Table 8.2: A summary of the SME responses, highlighting questions to which the SMEs responded with 'unsure', 'disagree', or 'strongly disagree'.

Type of validity		Verification target		Verification question	SME response score				Average per question
					SME 1	SME 2	SME 3	SME 4	
Construct	Content	Methodology	2.1	To what extent do you agree that the PVR-CMM has the potential to achieve the stated aim of the study?	4	4	4	4	80%
		Literature review	3.1	To what extent do you agree with the finding that the ICH E2B standard is the current best practice for reporting ADRs?	4	5	4	4	85%
			3.2	To what extent do you agree that the ICH E2B (R3) standard would support harmonization and interoperability of spontaneous reporting systems?	4	5	4	4	85%
	Face	DR1	4.1	The PVR-CMM can describe all activities relating to the spontaneous reporting of an ADR within PV.	4	5	4	4	85%
		DR2	4.2	The PVR-CMM enables the assessment of the maturity of an organisation's spontaneous reporting capabilities.	5	5	4	4	90%
		DR3	4.3	The PVR-CMM can be used to guide improvement initiatives.	5	5	4	4	90%
		DR4	4.4	The PVR-CMM is designed for the intended use by a specified target audience.	4	4	4	4	80%
		DR5	4.5	The PVR-CMM can be used for educational purposes and can be used to explain various aspects of the spontaneous reporting of ADRs to anyone with little to no background in PV.	3	3	4	3	65%
		DR6	4.6	The PVR-CMM is presented in an easy to understand manner and can be used by organisations to reach a common understanding of the system and the associated standards.	4	4	4	4	80%
		DR7	4.7	The PVR-CMM provides a set of domains, subdomains, and dimensions which characterise all aspects of spontaneous reporting of ADRs in PV.	4	4	4	4	80%
		DR8	4.8	The PVR-CMM is designed with STS theory in mind and therefore does not focus solely on the technical components of spontaneous reporting systems.	4	5	4	4	85%
		DR9	4.9	The capability statements of the PVR-CMM are mutually exclusive.	3	3	4	4	70%
		DR10	4.10	The capability statements of the PVR-CMM are collectively exhaustive.	3	4	4	3	70%
		DR11	4.11	The capability statements and maturity levels accumulate, with each level and statement encompassing the preceding lower levels and statements.	4	4	4	3	75%
				Average per SME	79%	86%	80%	76%	

[1] The Likert scale in the questionnaire, found in Appendix B.2, was adjusted to a 5 point scale, for the sake of consistency with the subsequent use of the 5 point Likert scale.

8.5.3 Points of interest: First verification

As shown in Table 8.2, none of the SMEs responded with 'strongly disagree' or 'disagree' to any of the questions. However, several responses of 'unsure' were provided, as shown by the highlighted cells. Three of the SMEs responded with 'unsure' to question 4.5, while two responded with 'unsure' to question 4.9 and question 4.10. Finally, one SME responded with 'unsure' to question 4.11. In this section, these responses will be further discussed, taking into consideration any additional comments provided by the SMEs on the self-completion questionnaire responses discussed in Section 8.5.4.

Question 4.5: The PVR-CMM could be used for educational purposes to explain the various aspects of spontaneous reporting to anyone with little or no background in pharmacovigilance.

SMEs one, two and four, were 'unsure' whether the PVR-CMM could be used for educational purposes to explain the various aspects of spontaneous reporting to anyone with little or no background in pharmacovigilance. To address this concern, an appendix labelled 'Appendix 1', will be added to the PVR-CMM in Section 9.2 (Note that 'Appendix 1' will form part of the PVR-CMM documentation and should not be confused with Appendices A, B and C of this dissertation). Appendix 1 will contain a summary of spontaneous reporting, with the aim of providing the PVR-CMM user with a foundational understanding of a spontaneous reporting system as well as what is meant by an interoperable system and what the associated objectives of such a system are.

Question 4.9: The capability and interoperability statements are mutually exclusive.

SMEs one and two were 'unsure' whether the capability and interoperability statements are mutually exclusive. SMEs three and four agreed that the capability and interoperability statements are mutually exclusive.

Question 4.10: The capability and interoperability statements are collectively exhaustive.

SMEs one and four were 'unsure' whether the capability and interoperability statements are collectively exhaustive. SMEs two and three agreed that the capability and interoperability statements are collectively exhaustive.

Question 4.11: The capability statements and maturity levels accumulate while encompassing the preceding statements and maturity levels.

SME four was 'unsure' whether the capability statements and maturity levels accumulate while encompassing the preceding statements and maturity levels. The remaining SMEs all

agreed that the capability statements and maturity levels accumulate while encompassing the preceding statements and maturity levels.

Regarding questions 4.9, 4.10 and 4.11, it should be acknowledged that the 'unsure' response from some of the SMEs could be due to their presumably limited previous exposure to the concept of CMMs, given their qualifications as stated in Table 8.1. In addition to this, a disadvantage of the self-completion questionnaire, is that the respondent cannot be prompted when experiencing difficulty in understanding or answering a question due to the absence of the interviewer. This may have been a contributing factor in these responses. Given that it would be impractical to ask an SME to verify 300 capability statements, the DRs seek to ensure that the capability statements are designed in such a way that they adhere to the basic principles of maturity model capability statements. In other words, by providing the SMEs with the DRs themselves, the SMEs can then verify the capability statements' adherence to the DRs, by considering a smaller sample size drawn from the total of 300 capability statements. To improve the subsequent iteration of the PVR-CMM, an additional DR was added, in response to the last three questions in the initial verification questionnaire. As discussed in Section 7.4, the additional DR is DR13: The descriptions of the capability statements clearly relate to and discriminate between maturity levels.

8.5.4 Additional comments from the first verification of the PVR-CMM

The following statements were made in response to the first verification of the PVR-CMM V1:

> "The aim of the study is to contribute towards the harmonisation of spontaneous reporting systems in the PV landscape. I think the use of the two maturity scales in the model will well define an organisation's capability maturity with regard to PV. How this contributes to harmonisation, I'm not 100% sure, but this is certainly a great first step. Follow up actions would be required by an organisation to initiate that harmonisation."

The latter portion of this comment raises a valid concern; that, without implementation and repeated use of the PVR-CMM, the model may not "contribute to harmonisation". The "follow up actions" which the comment refers to are indeed the repeated use of the PVR-CMM to make maturity assessments which highlight areas for improvement, thereby guiding the organisation towards harmonisation. The challenge with verifying this aspect of the PVR-CMM is that without a real-world implementation of the model, it would be impossible to determine the extent of the model's empirical validity. To determine the validity of the PVR-CMM, a case study was conducted at a later stage of this research, following the completion

of the verification activities described in this chapter. The case study is presented in Chapter 9 of this dissertation.

> "Well thought out and put together. The only reason I haven't strongly agreed with [some of] the [statements in the questionnaire] is because of the length of time it would take me to go through each dimension and scale. Nevertheless, impressive in the time I have. Well done."

This comment raises the concern that the PVR-CMM V1 does not meet the practical verification criterion described in Section 8.3.1. The PVR-CMM should allow for timely implementation, to inform the continuous improvement processes and guide decision-making. To address this, it is worthwhile considering a reduction in the number of dimensions included in the PVR-CMM. An additional proposed solution would be to change the physical layout of the PVR-CMM, so as to make the PVR-CMM more use-friendly, thereby reducing the probability of user error or fatigue. These two activities are subsequently addressed in Sections 8.6 and 9.2.

> "[The] guidelines aim to improve interoperability and harmonisation and I agree that the R3 has achieved this end, however we also need to be cognisant regarding the teething issues in implementation of the R2 vs R3? This includes compliance, system upgrades etc."

This comment provides insight into one of the primary concerns held by the MAHs; that is, how to guide the implementation of the new ICH E2B (R3) standard in a sustainable and efficient manner, so as to minimise the negative effects associated with inevitable "teething issues". As discussed at length in Chapter 5, this represents the rationale behind the use of many maturity models and frameworks. This comment could potentially be a result of the SME's unfamiliarity with the concept of maturity models.

> "It is a good concept to apply the CMM to PV activities. The author has developed a clear framework of the processes and levels of maturity. There is good literature review in terms of applicable CMM models in the healthcare domain. I agree that more streamlined and standardised PV activities [are] required, and that the E2B R3 aims to address the standardisation and interoperability within the EU. However, this remains a challenge even within an EU context, system changes, training, updating SOP's etc. which means more resources [required]/cost to company in the short and medium term. How would the [PVR-CMM] address efficiency and cost effectiveness? Another point would be a consideration of looking at region specific needs versus global. How do global challenges specifically translate into

> African context? Would the same infrastructure globally, be applicable relevant or available in a local African context?"

The latter part of this comment highlights some of the apparent limitations of the PVR-CMM. It is widely accepted that the strength of a good maturity model lies in it's ability to be generalised to various applications within a defined domain (De Bruin *et al.*, 2005; Pöppelbuß & Röglinger, 2011). By challenging the applicability of the PVR-CMM in an African context, the SME has simultaneously highlighted the need to test the PVR-CMM in a real-world implementation, as well as to engage with SMEs from other stakeholder groups such as National Regulatory Authorities. An additional DR was added in Section 7.4 in response to the two statements made above. The DR is DR12: The PVR-CMM can be used by stakeholders from various disciplines in PV to assess the spontaneous reporting of ADRs at the level in which they are engaged. This DR requirement recognises the various stakeholders that operate in different functions and capacities in a spontaneous reporting system, such as those involved in system infrastructure, training, and development of SOPs, etc.

This last comment, together with the other feedback received, resulted in the decision to subject the PVR-CMM to further verification testing, in order to increase the level of rigour in the PVR-CMM development, and the overall robustness of the final PVR-CMM.

8.5.5 Acknowledgement of limitations in verification process

Upon completion of the first verification of the PVR-CMM V1, a number of potential limitations in the verification process were identified. The three most notable limitations include:

1. A lack of diversity in the cohort of SMEs that were engaged to verify the PVR-CMM V1,

2. The difficulty associated with verifying the model content, such as the dimensions included and the capability statements, due to the large number of dimensions and statements and the time required to review them, and

3. Uncertainty regarding the generalisability of the PVR-CMM V1, and therefore the overall validity of the PVR-CMM V1, due to the lack of implementation of the model via an illustrative case study; with special reference to the model's validity in an African context.

The first and second limitations of the PVR-CMM V1 verification mentioned here, are addressed in the remainder of this chapter through more rigorous verification activities. The third limitation is addressed in Chapter 9.

8.5.5.1 Identifying a more diverse yet focused cohort of SMEs

To address the first potential weakness of the PVR-CMM V1, a larger quantity of SMEs with more diverse backgrounds had to be identified. To achieve this, the author attended a three day symposium and training event which brought together subject matter experts in PV from around the world to discuss PV in Africa. The event, hosted by the International Society of Pharmacovigilance (ISoP), together with the African Society of Pharmacovigilance (ASoP), was titled "Pharmacovigilance in Africa, beyond Spontaneous Reports". The event was the first of this kind organised in Africa, presented in Nairobi, Kenya; and addressed the specific needs and interests of people working in the field of PV either in regulatory authorities, pharmaceutical companies, in academia, hospitals or community settings. Amidst the various challenges associated with PV in Africa, the symposium and training event was focused on improving different components of safety regulatory systems and practices.

The faculty contributing to the symposium consisted of international and national experts in PV, representing government, academia, and industry. Given the specific focus of the symposium and the quality of the faculty members involved in the presentations and workshops, the symposium presented a unique opportunity to engage with experts to further verify and validate the PVR-CMM. Table 8.1 includes the details associated with the SMEs which were identified at the symposium, these additional SMEs are numbered from 5 through 14. It is important to recognise the diversity in the affiliations attributed to each of these SMEs as it was a priority to identify SMEs which represented not only MAHs but also RAs and the WHO. The newly identified cohort of SMEs represented various organisations and institutions including, but not limited to, two in academia, two WHO representatives, two representatives with considerable regulatory and policy experience from a top ten ranked independent multinational pharmaceutical and biotechnology company (Company 'B'; ranked by revenue), as well as three representatives from NRAs of African countries.

8.6 Second verification of PVR-CMM V1

The aim of the second verification of the PVR-CMM V1 was to engage with a larger cohort of SMEs to address the concerns raised in Sections 8.5.4 and 8.5.5. In Section 8.5.4, one of the SMEs drew attention to the fact that the PVR-CMM could be faced with challenges during implementation given the scale of the maturity model, more specifically the 300 capability statements associated with the 30 dimensions. To address this, the 30 dimensions of the PVR-CMM are subjected to a further round of verification with the purpose of determining which dimensions, if any, can potentially be removed from the PVR-CMM in order to simplify the model and improve its usability.

A further concern raised in Section 8.5.4, was that the first verification of the PVR-CMM V1 DRs, involved only SMEs from the MAH background. To address this, the SMEs identified at the ISoP-ASoP Mid Year Symposium in Nairobi, which represent a much more diverse cohort of SMEs, were requested to review the DRs of the PVR-CMM V1, and to propose any additional DRs that they considered to be worth including.

8.6.1 Verification questions: Second verification

Similarly to the first verification process, the questions presented to the SMEs in the second verification process aim to strengthen the PVR-CMM by addressing the face validity and content validity. To support the face validity, the SMEs numbered 5 through 12, were presented with the complete list of 13 DRs, with the addition of DR12 and DR13, as defined in Section 7.4. The SMEs were asked from their perspective whether or not the list of DRs was comprehensive, and which DRs should be added to strengthen the PVR-CMM in the subsequent iteration of development. In support of the content validity of the PVR-CMM, the complete set of 30 dimensions were presented to the SMEs, along with their respective contextual definitions and justification for inclusion. The SMEs were asked to what extent they agreed with the inclusion of the various dimensions in the PVR-CMM, in an effort to ascertain which dimensions, if any, could perhaps be removed from the PVR-CMM in the next iteration of development. The SMEs were also provided with a pre-reading document which provided them with an overview of the research leading to the development of the PVR-CMM.

During the symposium described in Section 8.5.5.1, every effort was made to engage with the SMEs in a face to face manner, this proved beneficial in that a significant amount of positive feedback and encouragement was received in response to the research overview, aims, and objectives. This feedback during personal communication, although undocumented, reaffirmed the value and necessity of the research, especially in the context of capacity building for PV in Africa. These face to face conversations also allowed the SMEs to ask any questions with regard to completing the second verification questionnaire. Due to the short duration of the symposium, the SMEs were provided with the questionnaires in the form of a hard copy and well as via email, which included an online version of the questionnaire.

8.6.2 Subject matter expert feedback: Second verification

Overall, the feedback from the second verification process was positive. The feedback will be discussed in two parts, relating to the two sections of the questionnaire. In response to the section addressing the comprehensiveness of the DRs, five of the responses shared the same sentiment, that the list of DRs was comprehensive. The remaining three SMEs provided

comments which required more reflection and response. The following statements were made by the eight SMEs[1]:

> "I think the design requirements are comprehensive enough."
>
> "The above list of offers a robust range of requirements."
>
> "All aspects are covered."
>
> "None that immediately come to mind. I know ethics has been mentioned but this, in my opinion, holds the key to enhancing Patient Safety across the world and across all institutions and stakeholders."
>
> "It is comprehensive, but [there is] a need to look at support systems for sustainability."

While all five of the above statements agree that the list of DRs in Section 7.4 is comprehensive, the fifth comment specifies a need to "look at support systems for sustainability". While this is a valid recommendation, the concept of sustainability is one typically associated with the use of maturity models to solve problems by developing capacity and increasing organisational maturity in a sustainable way, as conveyed in Chapter 5. Section 6.3 acknowledges the challenge associated with sustainability when implementing HIT solutions in health systems. The PVR-CMM also includes dimension 1.3.2 which refers to business sustainability practices in PV.

> "Capability to be versatile and be used for Active Safety Surveillance; Utility and capability for reporting Serious Adverse Events for investigational medicinal products used in clinical trials."

The contextualisation of this research is presented in Chapter 3. This research focusses on the post-marketing authorisation phase and the collection of safety data via spontaneous reporting of ADRs. In Section 3.2, the drug development process is described, indicating that clinical trials form part of the pre-marketing authorisation activities. Additionally, in Section 3.3, a distinction is made between active surveillance methods and passive surveillance methods, with spontaneous reporting being part of the latter. With that in mind, the SMEs comments regarding versatility for active safety surveillance and utility during clinical trials should be considered for possible inclusion in future iterations of the PVR-CMM, but at present, remain beyond the scope of this research .

[1]Note that the order in which these statements are presented in the dissertation does not necessarily correspond to the order in which the SMEs are listed in Table 8.1

> "I don't seem to feel a sense of patient perspective or involvement in the design. Also the Ministry of Health as a stakeholder could be beneficial as an implementer of the many recommendations. I was also wondering if media (social, print, radio, TV, etc) could be incorporated in one of the areas as administrative or data or IT concern."

The role of the patient, although perhaps difficult to identify in the context of the PVR-CMM assessment tool, has been described at length in Section 4.1.1 as well as in the level of analysis of PV as a sociotechnical system in Section 6.1.1. The concept of direct patient reporting is discussed throughout Chapter 4 and is addressed in the data capture dimension (dimension 2.1.1) of the PVR-CMM. In terms of the role of media, this has also been discussed in Section 4.1.1 and forms part of the PVR-CMM in dimension 1.4.3, human resources capacity development.

> "Not sure how the matrix will tackle some of the key barriers to reporting cases."

While the PVR-CMM is not developed with the primary intention of alleviating key barriers to reporting, every effort was made in studying the key barriers to reporting. Identifying the key barriers to reporting is the fourth research objective in this dissertation, as stated in Section 1.4.2. The design and development is cognisant of many of the key barriers to reporting, as discussed in Chapters 1, 3, and 4, with additional attention given to the sociotechnical challenges of introducing HITs to health systems in Chapter 6. The PVR-CMM does include a number of dimensions which seeks to address challenges relating to HCP knowledge and training, as well as the technologies used in reporting cases.

Table 8.3: Summary of SME responses in the verification of the PVR-CMM dimensions.

Dimension	SME 5	SME 6	SME 7	SME 8	SME 9	SME 10	SME 11	SME 12	Total score	Total score %	Mode	Median
Law, Regulation, and Policy	5	5	5	5	4	5	5	5	39	97,5%	5,0	5,0
Governance structures and commitment	5	5	4	5	5	4	5	5	38	95,0%	5,0	5,0
Business Continuity and Responsiveness	5	4	5	5	5	4	5	5	38	95,0%	5,0	5,0
Data ethics/Ownership	5	5	5	5	5	4	3	5	37	92,5%	5,0	5,0
Monitoring of performance and effectiveness	5	4	5	5	4	3	4	5	35	87,5%	5,0	4,5
Transparency and accountability	5	5	5	5	5	4	5	5	39	97,5%	5,0	5,0
Partnerships	5	5	5	5	3	5	4	5	37	92,5%	5,0	5,0
Stakeholder communication	4	5	5	5	4	4	5	5	37	92,5%	5,0	5,0
Organisational Strategy alignment	4	5	5	5	4	3	4	5	35	87,5%	5,0	4,5
Building a culture of Safety	5	5	5	5	5	4	4	5	38	95,0%	5,0	5,0
Organisational change management	4	5	5	5	4	4	5	5	37	92,5%	5,0	5,0
Financial management	5	5	5	5	4	4	5	4	37	92,5%	5,0	5,0
Financial resource mobilisation	4	5	5	5	3	4	5	4	35	87,5%	5,0	4,5
Regulatory Compliance	5	5	5	5	5	5	5	4	39	97,5%	5,0	5,0
Resource efficiency and business sustainability	5	5	5	5	4	4	4	5	37	92,5%	5,0	5,0
Data management	4	5	5	5	4	5	3	5	36	90,0%	5,0	5,0
Human resources policy	5	5	5	5	4	5	5	5	39	97,5%	5,0	5,0
Human resources capacity	5	5	5	5	4	5	5	5	39	97,5%	5,0	5,0
Human resources capacity development	4	5	5	5	5	5	5	5	39	97,5%	5,0	5,0
Data Capture	5	4	4	5	5	5	4	5	37	92,5%	5,0	5,0
Data Storage and Aggregation	5	5	4	5	5	4	4	5	37	92,5%	5,0	5,0
Workflows	5	5	5	5	4	4	5	5	38	95,0%	5,0	5,0
Data Presentation/Transmission	5	5	5	5	4	4	3	5	36	90,0%	5,0	5,0
Data Standards	5	5	5	5	4	3	5	5	37	92,5%	5,0	5,0
Information content	5	5	5	5	5	3	5	5	38	95,0%	5,0	5,0
Data protection, privacy, and security standards	5	5	5	5	5	3	5	5	38	95,0%	5,0	5,0
Information exchange and interoperability standards	5	5	5	5	5	4	5	5	39	97,5%	5,0	5,0
ICT Hardware	5	5	5	5	4	3	5	4	36	90,0%	5,0	5,0
Network	5	5	5	5	4	4	5	4	37	92,5%	5,0	5,0
Development and Maintenance	5	5	5	5	3	4	5	4	36	90,0%	5,0	5,0

Regarding the second section of the questionnaire, the SMEs were asked to what extent they agreed with the inclusion of each of the 30 dimensions in the PVR-CMM. Table 8.3 shows the responses from the eight SMEs numbered from SME five through twelve. The responses highlighted in red are those which represent a response of 'unsure'. Given that none of the 30 dimensions received more than one 'unsure' response, it was clear that all 30 of the dimensions should remain part of the PVR-CMM.

In addition to the results summarised in Table 8.3, the eight SMEs made the following comments:

> "IT infrastructure should not be for PV only but integrated to daily operations at patient care level."

> "Very well thought out approach - I like it."

> "Consider possibility of hosting the database in the "cloud" and new emerging options in ICT; also consider options of building the IT system as opposed to contracting or buying the software off the shelf."

Both the first, and second parts of this comment are suggesting the type of incremental improvements and use cases that are associated with the use of maturity models. By using the PVR-CMM it is envisioned that an organisation would increase it's data storage capabilities to the extent that new technologies, such as cloud-based storage and computing, are adopted. With regard to the second part of this comment, the case study in Chapter 9, considers the scenario where an organisation would use the PVR-CMM to develop its internal capabilities to the extent that it does not rely on 'off the shelf' software, this is specifically addressed in Section 9.4.

> "Some items on data seems to me would fit better in IT infrastructure or IT standards rather than business procedure or business objectives. I felt some of the dimension better suited other subdomains. For example, data presentation and transmission rather seem well suited for IT standards or infrastructure."

In response to this comment, it is important to consider the difference between business procedures and IT standards. Data presentation and data transmission are included in the business procedures because these are representative of what type of activities an organisation needs to execute to achieve their business objectives and remain within regulatory compliance. In terms of communicating PC data, whether by a regulator or an MAH, the key business procedures involved revolve around the receiving, capturing, storing, and sending of data. IT standards include documented, agreed upon, and repeatable ways of carrying out business procedures to improve their efficiency and effectiveness. The role of IT standards in the PVR-CMM is to support the execution of the associated business procedures.

> "Suggest hierarchical control analysis to demonstrate relations of different stakeholders and who is in control at different levels. It is difficult to judge whether this model with assess PV system maturity without testing it on a few examples."

Hierarchical control analysis would be a valuable analysis to carry out. However, within the context of this study, performing such an analysis remains beyond the scope of what is practically achievable, given the significant amount of time such an analysis would require. More on this suggestion is discussed in the future work section of this dissertation, found in Section 10.5.

8.7 Verification conclusion

Overall, positive feedback was received from all twelve of the SMEs. The results from the first verification, although positive, were deemed incomplete due to the lack of regulatory

representation among the SMEs. To address this, a second round of verification was performed, engaging a larger cohort of SMEs with more varied attributes. The results of the second verification, while resulting in minor refinements, corroborate the results of the first verification, indicating that the PVR-CMM V2 is verified and ready for implementation in a real-world setting. Additional comments from the SMEs included that the model was "impressive, well thought out and put together" (Appendix B.3.2), and that it is "a good concept to apply the CMM to PV activities" (Appendix B.3.3). Collectively, the results from the first and second verification activities indicate that the PVR-CMM V2 has the potential to achieve the aim and objectives which were stated in Sections 7.3 and 7.4. Comments relating to applicability of the model in region specific contexts, and more specifically the translation of problems from a global level to an African context, serve as inputs for the design and execution of the case study in Chapter 9.

8.8 Chapter 8: Conclusion

Following the population of the PVR-CMM V1, in Chapter 7, this chapter focussed on a verification and validation strategy, with the goal of ensuring the PVR-CMM's suitability for implementation in a real world setting. The PVR-CMM V1 was subjected to two verification processes, by engaging with subject matter experts and focussing on the design requirements and model components that made up the PVR-CMM V1. The feedback of the SMEs was incorporated so as to present the final iteration of the PVR-CMM in Chapter 9.

Chapter 9

Case study implementation and external validation

In this chapter the final version of the PVR-CMM, namely the PVR-CMM V2, is presented. The conception of transfer media is described, and the layout of the PVR-CMM V2 assessment tool is shown. The PVR-CMM V2 is subsequently implemented in a case study to determine the extent of empirical validity. The case study design, participating organisation, execution, and results, are discussed accordingly. Accompanying the results of the PVR-CMM V2 assessment results, are practical recommendations which seek to assist the participating organisation in improving their maturity across various dimensions. Finally, the PVR-CMM V2 is subjected to a validation activity, whereby the participating organisation is asked to validate the outcomes of the assessment against the PVR-CMM V2's stated aims; as well as the applicability of the PVR-CMM, and the overall acceptance of the PVR-CMM V2.

9.1 Introduction

This chapter discusses the case study which was executed using the second generation PVR-CMM, which was developed and refined in Chapters 7 and 8. The purpose of these chapters was to develop and refine the PVR-CMM by subjecting it to multiple rounds of verification, through the engagement of numerous SMEs. Once the model had been verified and refined, the next logical step was to apply the model in a maturity assessment case study.

Given the lengthy time horizon associated with the implementation of maturity models and maturity assessment frameworks, the PVR-CMM was not taken through a complete cycle of implementation. A complete cycle of implementation could require anywhere between one and two years to execute. For the purpose of this dissertation, the maturity model would be used to make an assessment of the organisation's maturity, followed by the development of practical recommendations which seek to guide the organisation towards a more mature overall state.

9.2 The PVR-CMM V2

Following the discussion of the SME feedback from the verification activities in Chapter 8, the final iteration of the PVR-CMM is presented in this chapter. The sixth phase in the PVR-CMM phases of development shown in Table 7.1, is the conception of transfer material. The conception of transfer refers to the method of transferring a maturity model to an organisation which seeks to use the maturity model to make a maturity assessment. In the case of the PVR-CMM V2, the conception of transfer media involved the transformation of the theoretical components and constructs of the model, together with the outcomes of the various phases of development and verification of the PVR-CMM, into a tangible and practicable assessment tool.

9.2.1 Conception of transfer media

The PVR-CMM V2 was constructed in Microsoft Excel (2016) as a workbook comprising 39 sheets. The 39 sheets are divided into three groups: (i) four introductory sheets; (ii) thirty sheets which capture the assessment data; and (iii) five sheets which display the results of the assessment. The complete PVR-CMM V2 is included in Appendix C.2, and a summary is presented via Figures 9.1 to 9.6.

The overall goal during the conception of transfer media is to create an assessment tool which facilitates the assessment procedure by improving the accessibility and usability of the PVR-CMM. The design and layout of the PVR-CMM V2 is intended to reduce user fatigue by keeping a consistent layout, allowing for simplified navigation throughout the assessment tool. The presentation of the PVR-CMM V2 in a staged manner is in response to the concerns raised by SMEs relating to the large number of dimensions and statements and the time required to review them. The inclusion of the four introductory sheets also serves to improve the users' knowledge and understanding of concepts such as spontaneous reporting systems, maturity models, and interoperability. This was deemed a necessary addition to the PVR-CMM V2 after considering the feedback from SMEs, particularly the feedback discussed in Section 8.5.3. To ensure that the users of the PVR-CMM V2 are fully conversant in the spontaneous reporting of ADRs, an appendix, namely Appendix 1 of the PVR-CMM was developed (found in Appendix C.1). This appendix is added to the PVR-CMM to address the question of whether the PVR-CMM can be used for educational purposes to explain the various aspects of spontaneous reporting to anyone with little or no background in pharmacovigilance. Appendix 1 is made up primarily from the contents of Chapters 3 and 4 and is therefore repetitive in the context of this thesis.

The landing page of the PVR-CMM V2 is the introduction sheet, shown in Figure 9.1. The introduction includes the aim and intended use of the assessment tool, as well as some background information relating to the development of the PVR-CMM. A disclaimer is included in the introduction so as to assist the user in understanding the intended use of the assessment tool, as well as to notify the user that the model may have to be tailored slightly to fit the needs of the individual or the organisation that is conducting the maturity assessment.

Figure 9.2 shows an overview of the PVR-CMM V2. The 30 dimensions are presented and grouped according to their respective domains and subdomains. By providing a high-level overview of the PVR-CMM V2 in such a way, the user is informed of the model's content and scope. This presents the user with an indication of what information might be required from the organisation, when conducting a maturity assessment.

Figure 9.3 shows the general maturity levels that are used in the PVR-CMM V2. This page in the assessment tool provides the user with definitions associated with the concepts of capability and interoperability. The generic maturity levels of both the capability and interoperability scales are provided so as to familiarise the user with the progression of maturity as well as to indicate how the maturity levels accumulate, in accordance with DR11, as stated in Section 7.4.

The user of the PVR-CMM V2 is provided with a set of instructions pertaining to the maturity assessment process, as shown in Figure 9.4. The instructions also inform the user how to navigate through the assessment tool by clicking the appropriate links. Below the instructions in Figure 9.4, is the profile page of the PVR-CMM V2. This profile section allows the user to capture information pertaining to the assessment which is being conducted. Information such as, the date, identification of the individual conducting the assessment, as well as information relating to the nature of the assessment, whether is it determined internally or externally, and within which department of which organisation. Upon completing the profile data entry, the user will begin the assessment by clicking the link at the bottom of the page.

Figure 9.5 shows the first dimension of the PVR-CMM V2. The layout of this page is consistent with the remaining 29 dimensions. The user is shown which dimension is being assessed, together with the contextual definition of the dimension and the respective sets of capability and interoperability statements. Once the user has read all of the necessary information, they can select from the drop-down list, the level description which most accurately describes the maturity of the dimension in question. Once the appropriate level description has been selected, the user can proceed to the next dimension by clicking the green arrow in the top right corner of the page.

The results page of the PVR-CMM V2 is shown in Figure 9.6. This page is automatically updated as the user progresses through the maturity assessment. The results are grouped according to the structure of the PVR-CMM as shown in the overview page, in Figure 9.2.

Note: *This document forms part of a larger project about pharmacovigilance, namely a PhD dissertation titled "Towards the interoperability of spontaneous reporting systems in pharmacovigilance: a maturity model approach with a sociotechnical system focus". © Maximillian Schurer, Louis Louw, Louzanne Bam, Imke de Kock; Department of Industrial Engineering, Stellenbosch University (Stellenbosch, South Africa).*

INTRODUCTION

The **Pharmacovigilance Reporting Capability Maturity Model** (PVR-CMM) is a maturity assessment tool which was developed to assist organisations which own or operate a spontaneous reporting system for pharmacovigilance. The aim of the model is to promote and improve interoperability by addressing the degree of integration of systems involved, providing guidance on which system components need to be improved, as well as providing a means for measuring interoperability progress accross the community of spontaneous reporting systems in the global pharmacovigilance landscape.

Spontaneous reporting of adverse drug reactions is widely considered to be the cornerstone of data generation in pharmacovigilance. Pharmacovigilance systems, by nature, are complex. Spontaneous reporting systems are faced with problems such as under-reporting and the communication of incomplete, unrepresentative, and uncontrolled data. The lack of standardisation and interoperability among these systems results in a reduced capability to detect and characterise new adverse drug interactions and reactions.

Maturity models assist organisations with linking their business objectives to the improvement goals they seek to achieve. By using this maturity assessment tool, an organisation can:

- Identify their current maturity level
- Identify a desired maturity level
- Benchmark and/or compare their capability maturity against a community of similar organisations
- Identify specific dimensions where potential improvement can be made
- Develop a roadmap or plan to grow the organisations maturity to the desired level

The development of the PVR-CMM was the culmination of an extensive multidisciplinary literature review covering aspects of pharmacovigilance, sociotechnical systems, interoperability, and maturity models. Through multiple validation processes with subject matter experts, the PVR-CMM has demonstrated value to organisations which own or operate a spontaneous reporting system.

Disclaimer: The PVR-CMM was developed with the intention of being used in conjunction with other PV related statutes, guidelines and documents. The contents of the PVR-CMM should be considered as general guidelines which can be adapted to suit the individual needs of any country or organisation managing a spontaneous reporting system for pharmacovigilance, while incorporating current best practices and achieving and maintaining regulatory compliance. The PVR-CMM lends support to other pharmacovigilance tools such as the WHO Global Benchmarking Tool and the Indicatior Based Pharmacovigilance Assessment Tool.

It is intended that the user of the PVR-CMM has a sufficient understanding of their organisations pharmacovigilance system so that the necessary adaptations and refinements to the tool can be made to fit the organisation's individual needs. The PVR-CMM has been developed to allow for enough generality to be widely applicable to organisations in pharmacovigilance, but also with enough specificity that it is possible to identify potential areas of weakness and strength. It was deemed necessary to simplify certain complex realities, at the sacrifice of accuracy in some cases, however, the best effort was made to avoid a too generic, vague, or too detailed and too complex approach. Although the covered topics are necessarily complex, simplicity in order to improve readability and applicability was paramount, with the intention of developing a tool which can be used to better understand the situation and define focused, specific strategies for improvement.

Finally, the PVR-CMM should by no means be considered perfect or even complete, it is expected that with feedback from users the model can be continuously improved, making it a better, more accurate tool. To send feedback, please see the note at the bottom of this page.

Please direct any feedback regarding this tool to:
16497457@sun.ac.za

Results

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Figure 9.1: The landing page and introduction of the PVR-CMM V2 assessment tool.

9. CASE STUDY IMPLEMENTATION AND EXTERNAL VALIDATION

Note: *This document forms part of a larger project about pharmacovigilance, namely a PhD dissertation titled "Towards the interoperability of spontaneous reporting systems in pharmacovigilance: a maturity model approach with a sociotechnical system focus". © Maximillian Schurer, Louis Louw, Louzanne Bam, Imke de Kock; Department of Industrial Engineering, Stellenbosch University (Stellenbosch, South Africa).*

OVERVIEW

The PVR-CMM is developed in such a way that it aims to be easily understood at a high level, with the details of capability maturity and interoperability maturity of the dimensions being addressed as the user delves deeper into the model.

Research suggests that interoperability results as a product of standardisation in four domains: technology, syntax, semantics, and pragmatics. The PVR-CMM is structured with sociotechnical system engineering principles in mind, that is to say, placing equal importance on the social, political, and environmental (workplace) factors. For these reasons, the 30 dimensions of the PVR-CMM (as seen below) are catagorised into 3 domains: Organisational (pragmatic), Informational (syntax and semantic), and Technical; as well as several subdomains.

The 30 dimensions which make up the PVR-CMM were selected from literature and have been subjected to multiple validation processes whereby subject matter experts from various pharmacovigilance organisations judged their inclusion in the model as critical to the success of a spontaneous reporting system in the global pharmacovigilance landscape. Explicitly, the 30 dimensions are:

Domain 1: Organisational

Subdomain 1: Leadership and Governance
- 1.1.1 Law, Regulation, and Policy
- 1.1.2 Governance structures and commitment
- 1.1.3 Business Continuity and Responsiveness
- 1.1.4 Data ethics/Ownership
- 1.1.5 Monitoring of performance and effectiveness
- 1.1.6 Transparency and accountability
- 1.1.7 Partnerships
- 1.1.8 Stakeholder communication
- 1.1.9 Organisational Strategy alignment
- 1.1.10 Building a culture of Safety
- 1.1.11 Organisational change management

Subdomain 2: Finance and Economics
- 1.2.1 Financial management
- 1.2.2 Financial resource mobilisation

Subdomain 3: Business Objectives
- 1.3.1 Regulatory Compliance
- 1.3.2 Resource efficiency and business sustainability
- 1.3.3 Data management

Subdomain 4: Human Resources
- 1.4.1 Human resources policy
- 1.4.2 Human resources capacity
- 1.4.3 Human resources capacity development

Domain 2: Informational

Subdomain 1: Business Procedures
- 2.1.1 Data Capture
- 2.1.2 Data Storage and Aggregation
- 2.1.3 Workflows
- 2.1.4 Data Presentation/Transmission

Subdomain 2: IT Standards
- 2.2.1 Data Standards
- 2.2.2 Information content
- 2.2.3 Data protection, privacy, and security standards
- 2.2.4 Information exchange and interoperability standards

Domain 3: Technical

Subdomain 1: IT Infrastructure
- 3.1.1 ICT Hardware
- 3.1.2 Network
- 3.1.3 Development and Maintenance

The overall maturity level of the system being assessed is represented by the collective maturity levels of these 30 dimensions. The results section of this tool will provide an overview of the maturity levels, as well as some graphical representations of the maturity levels across the various domains and subdomains.

MATURITY LEVELS

Please direct any feedback regarding this tool to:
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Results

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Figure 9.2: The overview page of the PVR-CMM V2 assessment tool.

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Maturity levels

The PVR-CMM makes use of two maturity scales, relating to capability maturity and interoperability maturity respectively. *Capability* is associated with specific business processes or a practice area within an organisation. Whereas, *maturity* is the degree to which an organisation has explicitly and consistently deployed processes, according to the business objectives. Interoperability can be defined as "the ability of different information technology systems and software applications to communicate, exchange data, and use information that has been exchanged".

The capability maturity levels that are used in the PVR-CMM are exactly the same as those originally developed by the well known CMMI Institute (2018):

CAPABILITY MATURITY		
LEVEL	**NAME**	**DESCRIPTION**
1	**Initial**	Initial approach to meeting the intent of the practice area.
2	**Managed**	Subsumes level 1. A simple, but complete set of practices that address the full intent of the practice area.
3	**Defined**	Builds on level 2. Uses organisational standards and tailoring to address project and work characteristics.
4	**Quantitatively Managed**	Builds on level 3. Uses statistical and other quantitative techniques to understand performance variation and detect, refine, or predict the area of focus to achieve quality and performance objectives.
5	**Optimizing**	Builds on level 4. Uses statistical and other quantitative techniques to optimise performance and improvement to achieve quality and process performance objectives.

The interoperability maturity scale used in the PVR-CMM is based on the work of Gottschalk (2009) and van Velsen *et al.* (2016):

INTEROPERABILITY MATURITY		
LEVEL	**NAME**	**DESCRIPTION**
1	**System as silo**	Single technology. No standardisation. Technical and semantic issues are solved.
2	**Peer-to-peer**	Two systems linked for simple exchange of data. Work processes are linked.
3	**Distributed** (Organisation bound, Inter-organisational)	Linking of homogenous systems for a common objective. Knowledge is shared.
4	**Integrated** (National; International)	Linking of heterogenous systems for a common goal. Benefits shared.
5	**Universal**	Systems can connect and disconnect freely and exchange data without serving a common goal.

INSTRUCTIONS

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Figure 9.3: The maturity levels of the PVR-CMM V2 assessment tool.

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INSTRUCTIONS

1) Complete the user profile form by clicking the link at the bottom of this page labelled "**PROFILE**"

2) When the profile form is complete, click the link at the bottom labelled "**BEGIN ASSESSMENT**"

3) Read the dimension definition and the maturity statements for both the *capability maturity* and the *interoperability maturity* scales

4) Identify which level description most accurately describes the maturity of the dimension in question

(*Please note that the level descriptions are based on generic situations, so "perfect matches" to your specific reality will be rare.*)

5) Click the drop-down list in the red outlined cell to select the level which you have identified

6) The number of the level and the description of the level will update accordingly

7) Click on the green arrow in the top right corner of the window to navigate to the next dimension

8) Repeat steps 3 - 7 until all of the dimensions have been assessed

9) When all of the dimensions have been assessed the top right corner of the screen will display "**RESULTS**", click here.

10) The results will be summarised and graphical representation of the results can be found using the appropriate links on the results page

PROFILE

PROFILE

Respondent details: (*All fields marked * MUST be completed)*

Date of assessment: *

Name of respondent: *

Role or position: *

Department: *

Organisation: *

Internal or External assessment: *

BEGIN ASSESSMENT

Figure 9.4: The instructions and profile pages of the PVR-CMM V2 assessment tool.

How to? **D1.1.1 Law, Regulation, and Policy**

The existence of the appropriate legal provisions that mandate and guide all PV related activities. Legal requirements and guidelines applicable to all National Competent Authorities/Regulatory Authorities and Marketing Authorisation Holders, regarding the collection, data management and reporting of suspected adverse drug reactions associated with medicinal products for human use. From an interoperability perspective it is necessary to have a common understanding of legislation relating to the exchange of information and the associated security and privacy issues. Legislation and regulatory guidelines must be compatible and define the boundaries of interoperability between two ICT systems.

CAPABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	INITIAL

LEVEL	NAME	DESCRIPTION
1	Initial	Some regulations are policies have been developed and implemented, but in an unstructured manner, lacking consistency.
2	Managed	Legislation has been developed to address patient safety, with a simple but complete set of regulations to support the legislation.
3	Defined	Regulations are tailored to support patient safety activities and policies are developed to ensure compliance.
4	Quantitatively Managed	Policies are developed to understand performance variation and detect, refine, or predict the area of focus to achieve quality and process performance objectives associated with patient safety.
5	Optimizing	All legislation and policies relating to patient safety are well defined, implemented, and actively reviewed and updated by a wide range of stakeholders.

INTEROPERABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	SYSTEM AS SILO

LEVEL	NAME	DESCRIPTION
1	System as silo	No formal legislation or policies. Any existing policies are localised to the individual system setting. No standardisation.
2	Peer-to-peer	Simple agreements between two homogenous systems are agreed upon to address simple business processes which are shared. Peer-to-peer.
3	Distributed	Legislation is fully distributed across all organisations/role players within the jurisdiction of the National Regulatory Authority. Linking of systems for a common objective.
4	Integrated	National legislation is fully integrated and aligned with international legislation. Policies are harmonised between organisations to share benefits and achieve value interoperability.
5	Universal	National legislation is fully integrated and aligned with international legislation. Legislation is continuously updated and improved upon and contributes to the development of the international legislative landscape.

MJ Schurer, L Louw, L Bam, IH de Kock

Results

Figure 9.5: The first of the 30 dimensions included in the PVR-CMM V2 assessment tool.

Maturity Assessment Results

The following results pertain to:

Organisation:

Assessment date:

Domain 1: Organisational				
Subdomain 1: Leadership and Governance	**Capability Level**	**Score**	**Interoperability Level**	**Score**
1.1.1 Law, Regulation, and Policy	Initial	1	System as silo	1
1.1.2 Governance structures and commitment	Initial	1	System as silo	1
1.1.3 Business Continuity and Responsiveness	Initial	1	System as silo	1
1.1.4 Data ethics/Ownership	Initial	1	System as silo	1
1.1.5 Monitoring of performance and effectiveness	Initial	1	System as silo	1
1.1.6 Transparency and accountability	Initial	1	System as silo	1
1.1.7 Partnerships	Initial	1	System as silo	1
1.1.8 Stakeholder communication	Initial	1	System as silo	1
1.1.9 Organisational Strategy alignment	Initial	1	System as silo	1
1.1.10 Building a culture of Safety	Initial	1	System as silo	1
1.1.11 Organisational change management	Initial	1	System as silo	1
	Subdomain Score:	**1,00**	**Subdomain Score:**	**1,00**
Subdomain 2: Finance and Economics	**Capability Level**	**Score**	**Interoperability Level**	**Score**
1.2.1 Financial management	Initial	1	System as silo	1
1.2.2 Financial resource mobilisation	Initial	1	System as silo	1
	Subdomain Score:	**1,00**	**Subdomain Score:**	**1,00**
Subdomain 3: Business Objectives	**Capability Level**	**Score**	**Interoperability Level**	**Score**
1.3.1 Regulatory Compliance	Initial	1	System as silo	1
1.3.2 Resource efficiency and business sustainability	Initial	1	System as silo	1
1.3.3 Data management	Initial	1	System as silo	1
	Subdomain Score:	**1,00**	**Subdomain Score:**	**1,00**
Subdomain 4: Human Resources	**Capability Level**	**Score**	**Interoperability Level**	**Score**
1.4.1 Human resources policy	Initial	1	System as silo	1
1.4.2 Human resources capacity	Initial	1	System as silo	1
1.4.3 Human resources capacity development	Initial	1	System as silo	1
	Subdomain Score:	**1,00**	**Subdomain Score:**	**1,00**
	Domain Score:	**1,00**	**Domain Score:**	**1,00**

Domain 2: Informational (Syntax and Semantics)				
Subdomain 1: Business Procedures	**Capability Level**	**Score**	**Interoperability Level**	**Score**
2.1.1 Data Capture	Initial	1	System as silo	1
2.1.2 Data Storage and Aggregation	Initial	1	System as silo	1
2.1.3 Workflows	Initial	1	System as silo	1
2.1.4 Data Presentation/Transmission	Initial	1	System as silo	1
	Subdomain Score:	**1,00**	**Subdomain Score:**	**1,00**
Subdomain 2: IT Standards	**Capability Level**	**Score**	**Interoperability Level**	**Score**
2.2.1 Data Standards	Initial	1	System as silo	1
2.2.2 Information content	Initial	1	System as silo	1
2.2.3 Data protection, privacy, and security standards	Initial	1	System as silo	1
2.2.4 Information exchange and interoperability standards	Initial	1	System as silo	1
	Subdomain Score:	**1,00**	**Subdomain Score:**	**1,00**
	Domain Score:	**1,00**	**Domain Score:**	**1,00**

Domain 3: Technical				
Subdomain 1: IT Infrastructure	**Capability Level**	**Score**	**Interoperability Level**	**Score**
3.1.1 ICT Hardware	Initial	1	System as silo	1
3.1.2 Network	Initial	1	System as silo	1
3.1.3 Development and Maintenance	Initial	1	System as silo	1
	Subdomain Score:	**1,00**	**Subdomain Score:**	**1,00**
	Domain Score:	**1,00**	**Domain Score:**	**1,00**

Figure 9.6: The results page of the PVR-CMM V2 assessment tool.

9.3 Case study: Implementation of the PVR-CMM V2

This section, together with Section 9.5, represent phase 7 of the PVR-CMM phases of development in Table 7.2; that is, implementation and validation. Upon completion of the transfer media, following the two verification activities, the PVR-CMM V2 is deemed ready for implementation in a real-world setting. To implement the PVR-CMM V2 in a case study, the design of the case study must be determined, a suitable participating organisation must be identified, and the validity of the maturity assessment outcomes must be ascertained to determine the generalisability of the maturity model.

Following the feedback received from SMEs during the second round of verification, discussed in Section 8.6, as well as discussions held with SMEs 13 and 14[1], it was decided that the PVR-CMM should be developed and implemented primarily within an African regulatory context. With this in mind, an appropriate participating regulatory authority had to be identified.

9.3.1 Case study participating organisation

For this case study, a prominent National Pharmaceutical Regulatory Authority within the Southern African Development Community (SADC) was approached. The regulatory authority has been conducting PV activities for over 40 years, having been among the first African countries to join the WHO IDMP, in the early 1990's. The regulatory authority coordinates the national pharmacovigilance programme, which includes 3 national PV centres, as well as a national ADR monitoring unit which was created in the late 1980's. In 2015, the regulatory authority reported spontaneous reporting rates of approximately 62 reports/million capita. The vigilance and post-marketing surveillance working group of the RA is tasked with establishing a regimen of vigilance for the collection and evaluation of information relevant to the benefit to risk balance of medicines and medical devices on the market within it's jurisdiction. As well as, the continuous monitoring of the safety profiles of these products and taking appropriate action where necessary.

Given the scale of a case study of this nature, as well as the limited number of national regulatory authorities within a reasonable geographical proximity, it was deemed that one thorough case study would suffice to demonstrate the applicability and value of the PVR-CMM.

A letter of request for the case study was sent to the regulatory authority, which can be found in Section C.3, of Appendix C. The letter serves to inform the organisation of the purpose of the case study. It also communicates the time and materials that are necessary to conduct the case study. Upon receipt of the letter, the organisation invited the researcher to present the

[1] Conversations occurring during the ISoP-ASoP symposium in Nairobi, Kenya.

findings of this dissertation as well as a proposal presentation to various representatives of the organisation's executive body. Upon delivering this presentation the director granted approval for the commencement of the case study.

9.3.2 Case study execution

The case study was conducted over a period of five days at the location of the national regulatory authority and comprised a series of contact sessions with the appropriate members of the organisation. In total, four sessions of 3 hours were conducted, resulting in one complete assessment of the organisation's maturity. Each session involved at least 3 people, the facilitator, as well as two members of the regulatory authority. During the maturity assessment, relevant members of the vigilance unit were invited to provide information pertaining to dimensions which they were more directly involved in. Throughout the sessions, three members of the organisation were exposed to the entire maturity assessment process, including all 30 dimensions of the PVR-CMM. These three representatives, henceforth referred to as participants 1, 2, and 3; included two medicines control officers (P1 and P2), as well as the deputy director of the pharmacovigilance unit (P3).

If at any point during the maturity assessment process, the participants were in a state of disagreement as to which maturity level to ascribe to a particular dimension, a note was made and the final decision was left to the discretion of P3, given P3's seniority within the organisation. Throughout the assessment, the evidence provided in support of each capability maturity level and interoperability maturity level selected, was recorded. For the protection of the regulatory authority's identity, this detailed information is not included in the dissertation.

Upon completion of the maturity assessment, the results are discussed and practical recommendations are developed in Section 9.4.

9.4 Case study results and practical recommendations

The results of the maturity assessment, as generated by the PVR-CMM V2, are displayed in Table 9.1, as well as in various radar charts in Figures 9.7 to 9.11. Following Table 9.1, the discussion of the results will be structured according to the radar charts as well as the following criteria:

1. Dimensions which score a maturity level below the average capability maturity or interoperability maturity score;

2. Dimensions which score the lowest combined capability maturity and interoperability maturity scores, in other words, the weakest dimensions;

3. Dimensions with the greatest absolute difference between capability maturity and interoperability maturity;
4. Subdomains with the lowest average capability maturity;
5. Subdomains with the lowest average interoperability maturity; and
6. Subdomains with the greatest absolute difference between average capability maturity and average interoperability maturity.

9. CASE STUDY IMPLEMENTATION AND EXTERNAL VALIDATION

Table 9.1: Case study maturity assessment results.

Maturity Assessment Results

The following results pertain to:

Organisation: [redacted]

Assessment date: [redacted]

Domain 1: Organisational				
Subdomain 1: Leadership and Governance	**Capability Level**	**Score**	**Interoperability Level**	**Score**
1.1.1 Law, Regulation, and Policy	Managed	2	System as silo	1
1.1.2 Governance structures and commitment	Quantitatively Managed	4	Distributed	3
1.1.3 Business Continuity and Responsiveness	Initial	1	System as silo	1
1.1.4 Data ethics/Ownership	Defined	3	Peer-to-peer	2
1.1.5 Monitoring of performance and effectiveness	Defined	3	Peer-to-peer	2
1.1.6 Transparency and accountability	Managed	2	Peer-to-peer	2
1.1.7 Partnerships	Managed	2	Peer-to-peer	2
1.1.8 Stakeholder communication	Managed	2	Peer-to-peer	2
1.1.9 Organisational Strategy alignment	Managed	2	Peer-to-peer	2
1.1.10 Building a culture of Safety	Defined	3	Peer-to-peer	2
1.1.11 Organisational change management	Defined	3	Peer-to-peer	2
	Subdomain Score:	**2,45**	**Subdomain Score:**	**1,91**
Subdomain 2: Finance and Economics	**Capability Level**	**Score**	**Interoperability Level**	**Score**
1.2.1 Financial management	Quantitatively Managed	4	System as silo	1
1.2.2 Financial resource mobilisation	Managed	2	System as silo	1
	Subdomain Score:	**3,00**	**Subdomain Score:**	**1,00**
Subdomain 3: Business Objectives	**Capability Level**	**Score**	**Interoperability Level**	**Score**
1.3.1 Regulatory Compliance	Quantitatively Managed	4	Integrated	4
1.3.2 Resource efficiency and business sustainability	Defined	3	Integrated	4
1.3.3 Data management	Defined	3	Peer-to-peer	2
	Subdomain Score:	**3,33**	**Subdomain Score:**	**3,33**
Subdomain 4: Human Resources	**Capability Level**	**Score**	**Interoperability Level**	**Score**
1.4.1 Human resources policy	Quantitatively Managed	4	System as silo	1
1.4.2 Human resources capacity	Defined	3	Peer-to-peer	2
1.4.3 Human resources capacity development	Quantitatively Managed	4	System as silo	1
	Subdomain Score:	**3,67**	**Subdomain Score:**	**1,33**
	Domain Score:	**3,11**	**Domain Score:**	**1,89**

Domain 2: Informational (Syntax and Semantics)				
Subdomain 1: Business Procedures	**Capability Level**	**Score**	**Interoperability Level**	**Score**
2.1.1 Data Capture	Managed	2	Peer-to-peer	2
2.1.2 Data Storage and Aggregation	Managed	2	Peer-to-peer	2
2.1.3 Workflows	Defined	3	System as silo	1
2.1.4 Data Presentation/Transmission	Quantitatively Managed	4	Universal	5
	Subdomain Score:	**2,75**	**Subdomain Score:**	**2,50**
Subdomain 2: IT Standards	**Capability Level**	**Score**	**Interoperability Level**	**Score**
2.2.1 Data Standards	Managed	2	Peer-to-peer	2
2.2.2 Information content	Managed	2	Distributed	3
2.2.3 Data protection, privacy, and security standards	Managed	2	Peer-to-peer	2
2.2.4 Information exchange and interoperability standards	Initial	1	System as silo	1
	Subdomain Score:	**1,75**	**Subdomain Score:**	**2,00**
	Domain Score:	**2,25**	**Domain Score:**	**2,25**

Domain 3: Technical				
Subdomain 1: IT Infrastructure	**Capability Level**	**Score**	**Interoperability Level**	**Score**
3.1.1 ICT Hardware	Managed	2	System as silo	1
3.1.2 Network	Defined	3	Peer-to-peer	2
3.1.3 Development and Maintenance	Managed	2	System as silo	1
	Subdomain Score:	**2,33**	**Subdomain Score:**	**1,33**
	Domain Score:	**2,33**	**Domain Score:**	**1,33**

To identify the dimensions for which to provide practical recommendations, the criteria stated above will be used. It is important to note that the recommendations included in this report were formulated with the inputs and experiences gained via the maturity assessment which was conducted with the regulatory authority. Ideally, the organisation conducting the maturity assessment recognises the fact that the work does not come to an end once the maturity assessment has been conducted. Rather, the PVR-CMM maturity assessment would be conducted on a regular basis by the organisation, where the organisation recognises the cyclical nature of assess, analyse, improve. Following each maturity assessment, a set of improvement initiatives would be developed by the organisation with the help of the PVR-CMM. Even if the organisation considers the improvement initiatives not worth the associated implementation costs, the PVR-CMM can still be used to monitor and manage the maturity of its processes.

Given that this maturity assessment was conducted as a part of a case study, the following recommendations have been developed by someone external to the regulatory authority, therefore the recommendations are limited to the extent that the author of the PVR-CMM does not have the necessary understanding of the organisation. However, the best effort was made to offer recommendations for improvement. It is envisioned that if the organisation was to use the PVR-CMM as it is intended to be used, the organisation would be sufficiently guided by the PVR-CMM contents, to develop more thorough and organisation-specific improvement initiatives.

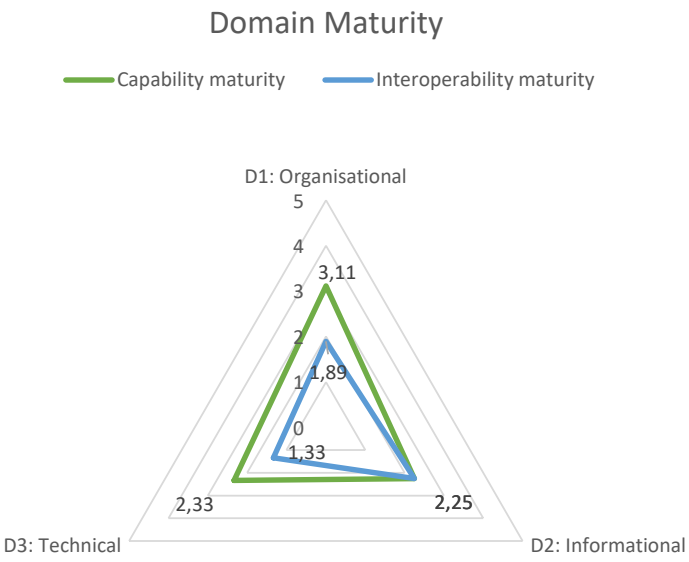

Figure 9.7: Radar chart showing the domain maturity levels from the case study.

At the domain level, shown in Figure 9.7, it is evident that in general the interoperability maturity of the RA is lagging behind the capability maturity. The only exception to this, at a

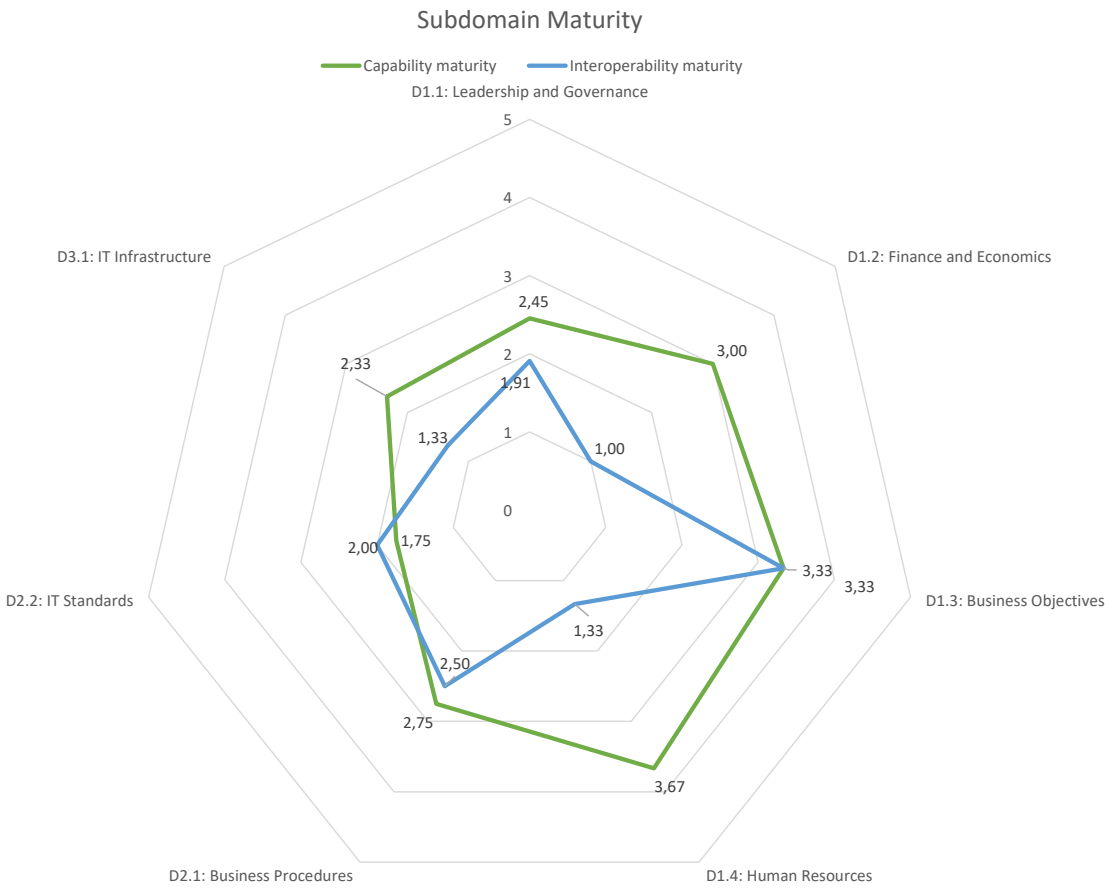

Figure 9.8: Radar chart showing the subdomain maturity levels from the case study.

domain level, is the interoperability maturity of the informational domain. The reason for this can most likely be attributed to the RA's reliance on the VigiFlow software to send and receive ICSRs. As the regulatory authority currently uses VigiFlow, one could argue that their capability and interoperability maturity in terms of the informational domain is high. A perspective that was adopted during the assessment, however, is that if the RA were to stop their VigiFlow subscription, the capability and interoperability maturity would be considerably lower. With the exception of the data presentation/transmission dimension, all of the dimensions in the informational domain were assessed under the context of the RA not having an active VigiFlow subscription. The logic here was to assume that without VigiFlow, the PVR-CMM V2 could help to improve the informational domain to the extent that the RA would no longer rely on VigiFlow as the primary ICSR gateway, much like the case of Eudravigilance software in EU and FAERS software in US. These are ICSR gateways that comply with VigiFlow standards but offer significantly more functionality tailored to the region's needs and priorities.

At the subdomain level, shown in Figure 9.8, observations with respect to sixth criterion are highlighted. The subdomains with the greatest absolute difference between average capability

maturity and average interoperability maturity are:

1. D1.2: Finance and economics, with an absolute difference of 2.0; and,
2. D1.4: Human resources, with an absolute difference of 2.33.

An additional observation is the interoperability maturity of subdomain D2.2: IT standards, this is the only subdomain in the entire maturity assessment which scored a greater level of interoperability maturity than capability maturity. The subdomains with below average maturity levels for capability maturity and interoperability maturity, respectively, include:

1. D1.1: Leadership and governance;
2. D2.1: Business procedures;
3. D2.2: IT standards; and,
4. D3.1: IT infrastructure.

And for interoperability maturity, the subdomains which scored the lowest include:

1. D1.1: Leadership and governance;
2. D1.2: Finance and economics;
3. D1.4: Human resources; and,
4. D3.1: IT infrastructure.

9.4.1 Domain 1 results and recommendations

Domain 1, shown in Figure 9.9, contains three of the overall weakest dimensions in terms of their combined capability and interoperability maturity levels (criterion 2), these three dimensions are:

1. D1.1.1: Law, regulation, and policy;
2. D1.1.3: Business continuity and responsiveness; and,
3. D1.2.2: Financial resource mobilisation.

The dimensions in domain 1 with the greatest difference between their capability maturity level and their interoperability maturity level (criterion 3), include:

1. D1.2.1: Financial management;
2. D1.4.1: Human resources policy; and,

3. D1.4.3: Human resources capacity development.

Additional dimensions in domain 1 which scored below the average capability or interoperability maturity level (criterion 1), include:

1. D1.1.6: Transparency and accountability;
2. D1.1.7: Partnerships;
3. D1.1.8: Stakeholder communication; and,
4. D1.1.9: Organisational strategy alignment.

Subdomain D1.1 scored the lowest average capability maturity level (criterion 4). In terms of interoperability maturity, subdomains D1.1, D1.2, and D1.4, scored below the average subdomain interoperability maturity across all domains (criterion 5).

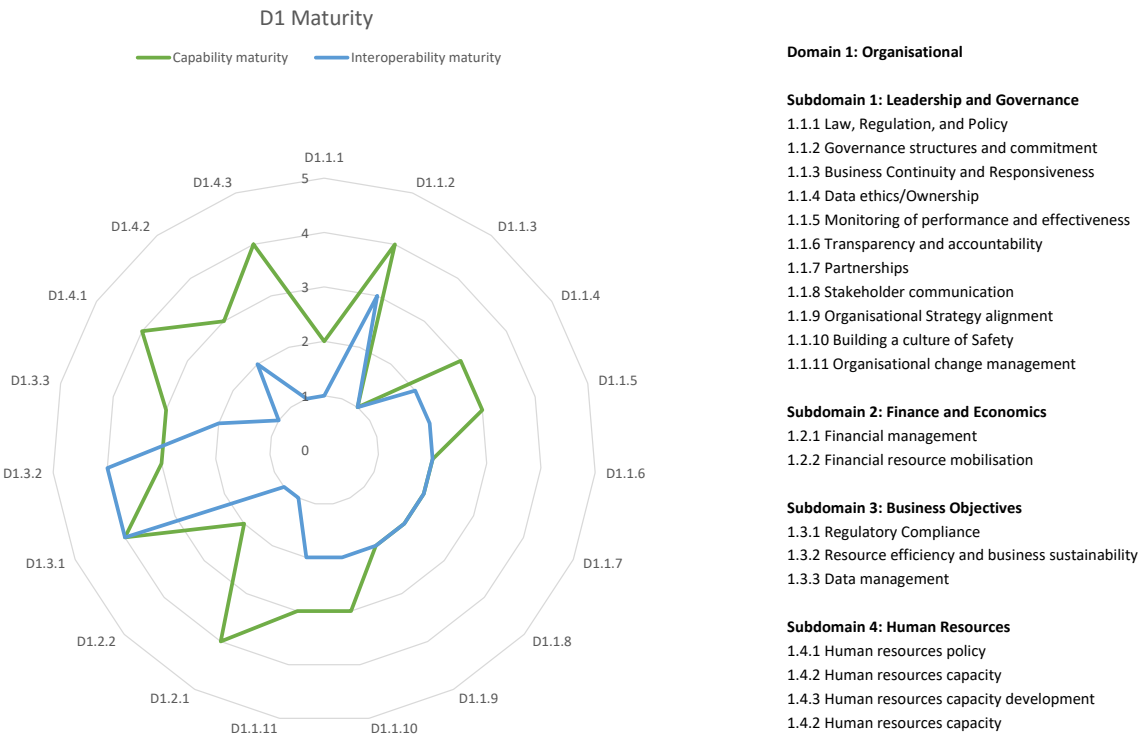

Figure 9.9: Radar chart showing the dimension level of domain 1 maturity levels from the case study.

The practical recommendations with regard to the dimensions in domain one, identified here, are as follows:

Dimension 1.1.1 Law, regulation and policy

The term vigilance was only recently added to the legal framework of the national regulator, through an amendment Act made in 2015. This implies that pharmacovigilance has not been addressed with a high degree of specificity. Recommendations would be to follow the example of the European Medicines Agency and develop a more comprehensive pharmacovigilance legal framework. The aim of such a framework would be to reduce the number of ADRs in a country, this would be achieved through (European Medicines Agency, 2012):

- the collection of better data on medicines and their safety;
- rapid and robust assessment of issues related to the safety of medicines;
- effective regulatory action to deliver safe and effective use of medicines;
- empowerment of patients through reporting and participation; and
- increased levels of transparency and better communication.

The pharmacovigilance legal framework should also seek to impact marketing authorisation applicants and holders, by (European Medicines Agency, 2012):

- making their roles and responsibilities clear;
- minimising duplication of effort;
- freeing up resources by rationalising and simplifying reporting on safety issues; and
- establishing a clear legal framework for post-authorisation monitoring.

Practical measures to facilitate the performance of pharmacovigilance in accordance with the legislation should be developed and implemented, as is the case with the good pharmacovigilance practice guidelines of the EMA.

Dimension 1.1.3 Business continuity and responsiveness

The recommendation here would be to develop a business continuity plan to enable the regulatory authority to continue to deliver its services through a major disruption. To do this, the regulatory authority would need to determine a range of threat scenarios, then plan and document how the organisation would continue to function through those incidents. The business continuity plan can also include a disaster recovery plan, which would describe how the organisation recovers from a significant disruption. The following six steps can be taken to develop a business continuity plan (Adapted from (Cerullo & Cerullo, 2004)):

1. Business Impact Analysis, to identify the critical business operations and processes, as well as the resources which support them.

2. Identify principle classes of threat and the impact that they may have on the organisation. These can be collated into a small number of archetypal scenarios, to assist with later training and testing of the business continuity plan.

3. Take action to mitigate those risks. This is not strictly part of business continuity planning, but it is recommended to carry it out at this stage of the process.

4. To create readiness plans to maintain continuity in the face of the threat that has been identified. Typically, these are threats to people, to physical infrastructure, and to technology and data.

5. To identify a core team of business continuity leaders. Conduct training, tests and exercises to allow the organisation to evaluate the plans and to increase preparedness.

6. Maintain the plan and keep it under review, as part of a continuous business continuity planning cycle.

Dimension 1.1.6 Transparency and accountability

Transparency and accountability should be understood by all members of the organisation. The organisation should have strong policies in place to address the transparency of their business practices and to understand the value of maintaining a positive sentiment by the external environment. Upon completing the PVR-CMM maturity assessment, it was evident that the organisation had recognised the need to make information publicly available. In addition to current methods such as "Dear HCP[1]" letters and newsletters, it is recommended that the following three categories of information be made available in the public domain to enable accountability:

1. Standards and commitments: These include legislation, regulations, policies and SOPs.

2. Decisions and results: Decisions made by committees, declarations of interest, current projects, package amendment details, progress reports on policy commitments, audit reports, KPIs.

3. Consequences and responsive actions: These include follow ups of investigated complaints and a list of corrective actions taken.

[1]SAHPRA defines a "Dear HCP" letter as "a letter distributed by an applicant or a holder of a certificate of registration for a medicine to medical practitioners and other health care professionals to convey important information about medicines. Such letters can be requested by the regulator or initiated by the applicant (South African Health Products Regulatory Authority, 2015).

A further recommendation would be to make use of the Pharmaceutical System Transparency and Accountability Assessment Tool published by the World Health Organisation in 2018.

Dimension 1.1.7 Partnerships

Pharmacovigilance is a collaborative endeavour; therefore the organisation should seek to form partnerships which provide complementary expertise. Currently the organisation takes part in Industry Task Group (ITG) meetings to discuss pharmacovigilance. The organisation has identified potential partnerships with the national Medicines Information Centre (MIC) as well as the national poison centre. These partnerships should be managed so as to establish trust between the partnering organisations. Partnerships between PV collaborating centres are also important for sharing of information and the development and adoption of best practices. The organisation should actively seek out partnerships which can bring together the necessary diversity of expertise to strengthen the pharmaceutical system.

Dimension 1.1.8 Stakeholder communication

Currently the organisation has strong communication with industry but is still in the process of establishing formal communication channels with its provincial constituents. Stakeholder communication consists of three components. The recommendation here is to identify stakeholders, perform a stakeholder analysis, and finally, manage the stakeholder relationships. Regular communication with key stakeholders helps to create positive and long-standing relationships, which inevitably result in a range of benefits for an organisation. Formal communication channels must be established between key stakeholders, whether internal or external, such as the regulator, health authority, clinicians, MAHs and patients.

Active stakeholder engagement with stakeholders from various system perspectives such as end-users, IT, or business management, would contribute to the success of health information technology solutions in achieving interoperability. Adoption mechanisms such as awareness campaigns, financial incentive programmes, and professional development and accreditation programmes should also be considered.

Dimension 1.1.9 Organisational strategy alignment

Organisational alignment is important as there can be departmental boundaries within the organisation which may impede interactions relating to PV. A further recommendation would be that organisations create a multidisciplinary PV team to foster collaboration between the various departments of the organisation. Clearly defined roles and responsibilities within the organisation should be created for the entire drug development and post-marketing stages of the product life cycle. In doing so, a clear chain of communication and command is established, which contributes to accountability and assists with decision-making. Based on the results of

the PVR-CMM assessment, it is evident that a siloed mentality exists within the organisation. The organisation should seek to share a common understanding of vigilance, and its role in various working groups such as pharmaceutical regulation, veterinary science, and medical devices.

Dimension 1.2.1 Financial management

The interoperability of this dimension was difficult to interpret in this case. The main challenge that was identified was the lack of communication and visibility of financial management activities between different provinces, due to the differences in provincial government. In the case of VigiFlow, the organisation encourages provinces to adopt the technology and is able to provide requirement specifications to each province for the adoption of VigiFlow. However, the organisation has no influence over budgets and the acquisition of finances at a provincial level. Given that financial management strategies of various provinces are isolated, the dimension was scored as level 1 for interoperability.

Dimension 1.2.2 Financial resource mobilisation

Financial resource mobilisation includes all activities relating to securing new and additional financial resources for an organisation. The organisation is currently working on a project with a top global management consulting firm, this project was made possible via a grant from the Bill and Melinda Gates Foundation. Strategies to acquire additional financial grants similar to the Bill and Melinda Gates Foundation grant should be investigated. Additionally, the organisation should attempt to engage with national government to formalise regular financial provisions. It is also potentially worthwhile to assist provincial partners in managing their financial resources so as to facilitate the implementation of hardware and software upgrades, such as making use of the VigiFlow system.

To initiate a financial resource mobilisation strategy, the organisation should identify potential sources of funds, actively solicit pledges from donors and funders, follow up on pledges to obtain the funds, deposit the funds and maintain records detailing the transactions and restrictions of the usage of the funds.

Dimension 1.4.1 Human resources policy

The results of the PVR-CMM maturity assessment indicate that the organisation does not have an internal human resources department. The HR policies are developed by the department of health. The recommendation for this dimension is for the organisation to develop a human resources policy which addresses the specific needs and goals of the organisation and includes a set of principles, guidelines, and norms that the organisation adopts to help manage its employees.

Dimension 1.4.3 Human resources capacity development

Organisations should seek to acquire and retain PV personnel with varied and diverse expertise and skill sets. Human resource managers should adapt their talent management approach so as to identify, acquire, and develop talent which can continually meet the ever-changing expectations of PV. In addition to improving collaboration between departments, it is envisioned that the PV teams of the future will consist of medical and science professionals, statisticians, computer scientists, and IT developers.

Currently the organisation has no influence over the medical curricula in the country, but is investigating ways to grow its involvement in this regard. The organisation has been involved in training of HCPs in a number of provinces, to assist with the adoption of the VigiFlow system. It was noted during the maturity assessment that the organisation is reluctant to offer training in public health programs due to concerns of confusing HCPs who are receiving parallel training from different stakeholders. An additional need which was identified was the need to create awareness of the organisation among HCPs across the country. The recommendation for this dimension is to incorporate patient safety outcomes in the curriculum of HCPs, which must be supported by continuous evaluation and assessment during their professional careers. In addition to education and training, medical training institutions should seek to address the blame culture that is present in PV.

9.4.2 Domain 2 results and recommendations

Domain 2, shown in Figure 9.10, contains one of the overall weakest dimensions in terms of their combined capability and interoperability maturity levels (criterion 2), D2.2.4: Information exchange and interoperability standards. The dimension in domain 2 with the greatest difference between it's capability maturity level and their interoperability maturity level (criterion 3), is D2.1.3: Workflows.

Additional dimension in domain 2 which scored below the average capability or interoperability maturity level (criterion 1), include:

1. D2.1.1: Data capture;
2. D2.1.2: Data storage and aggregation;
3. D2.2.1: Data standards;
4. D2.2.2: Information content; and,
5. D2.2.3: Data protection, privacy, and security standards.

9. CASE STUDY IMPLEMENTATION AND EXTERNAL VALIDATION

Both subdomains D2.1 and D2.2 scored amongst the lowest average capability maturity levels (criterion 4).

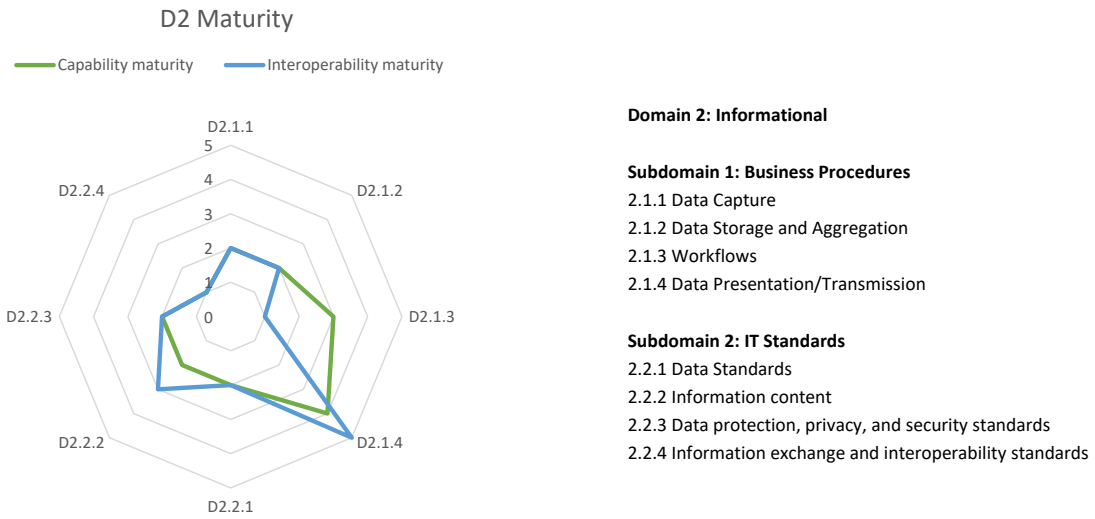

Figure 9.10: Radar chart showing the dimension level of domain 2 maturity levels from the case study.

The practical recommendations with regard to the dimensions in domain two, identified here, are as follows:

Dimension 2.1.1 Data capture

Currently there is a mixed approach when it comes to data capture in the country. There is a mobile application which was developed for primary healthcare which includes the national standard ADR reporting form. This mobile application is primarily used by HCPs to support other work functions, not necessarily to report ADRs. The ADRs that are reported via this method still need to be re-captured for entry into the VigiFlow system. The organisation has identified the need for a mobile application exclusively for ADR reporting, but there are challenges associated with adaptation for local implementation settings. In addition to paper forms received from HCPs, the organisation also receives ADR reports in various formats from MAHs, such as E2B compliant forms and CIOMS forms. Often these reports are sent as email attachments, which can sometimes present a challenge to the organisation in terms of readability. The recommendation for this dimension is to establish a standardised electronic form for capturing data, one which is compliant with the E2B (R3) standard and therefore the VigiFlow system too.

Dimension 2.1.2 Data storage and aggregation

The storage of paper files is currently being outsourced to a third-party organisation. The organisation does make use of the Vigibase database, for cost saving purposes. However, currently there is no existing internal database for ICSRs and the organisation has identified a need for a cloud-based storage system.

Dimension 2.1.3 Workflows

Workflows which were not organised to be interoperable was identified as one of the most prominent challenges for the organisation. Workflows typically involve the use of Standard Operating Procedures (SOPs). In the context of a spontaneous reporting system this includes receiving the information, case entry, duplicate checking, case registration, case triage, data entry and narrative write up, review, case closure and the transmission of the ICSR.

Dimension 2.2.1 Data standards

The recommendation for this dimension is that the organisation adopts a comprehensive portfolio of data standards which relate to the exchange of electronic healthcare data. However, it is important to be aware of the fact that due to the complex interactions of business processes, international legislation, and varying system requirements in the global PV landscape, the notion of 'plug and play' standards for interoperability is not as straightforward as it would appear. For this reason, the HIT implementation teams need to adapt their approach to fit their system requirements, while remaining mindful of the goal of interoperability. In general, standardisation through the implementation of HITs requires adaptation that varies from one context to the next. This adaptation can be guided and informed via the identification of use cases. Use cases are commonly used in software and systems engineering to define the interactions between an actor and a system to achieve a goal.

Dimension 2.2.2 Information content

For this dimension the organisation was scored a level 2, which is characterised by the existence of an ICSR form with a simple but complete set of basic data elements which constitute the minimum acceptable information. A level 3 in this dimension assumes the adoption of an electronic reporting form, which the organisation does not comply with currently. However, once the organisation has progressed to the wide scale adoption of electronic reporting, a level 3 will be attained if the electronic reporting form complies with standards such as E2B (R3) and the Minimal Information Model for Patient Safety (MIM PS) standard.

Dimension 2.2.3 Data protection, privacy, and security standards

Documents containing sensitive PV data should not be left unattended. It is recommended that the organisation adopt a clear desk policy for PV documents. A clean desk policy is one which ensures all sensitive and confidential data is stored and protected from unauthorised viewing.

Individuals that work with documents containing sensitive PV data should take appropriate measures against unauthorised access to the data. The organisation must identify and adhere to a specific set of data protection, privacy, and security standards. Currently, some standards are incidentally and unpredictably adhered to. The organisation makes use of a secrecy clause and has simple agreements with third party companies that store the ADR paper files for long term storage. Discarded ADR reports are shredded via a shredding company. If the organisation makes use of a cloud-based storage system for electronic ICSR information, it must be fully protected so as to ensure access to the data can be restricted to named individuals. Sensitive data should be encrypted to ensure the integrity of data transmissions. Currently, information is aggregated so as to anonymise the data for inclusion in quarterly reports.

Dimension 2.2.4 Information exchange and interoperability standards

It was noted during the PVR-CMM maturity assessment that this dimension assumes the organisation has a sufficient capability for electronic reporting. For this reason, there is no practical recommendation that is justified in this instance. However, with repeated use of the PVR-CMM and by conducting regular maturity assessments in between improvement initiatives, it is envisioned that this dimension will become relevant to the organisation.

9.4.3 Domain 3 results and recommendations

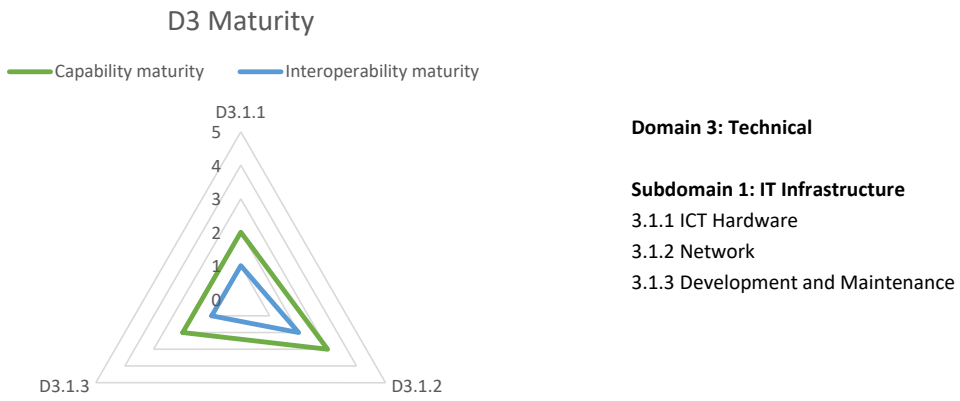

Figure 9.11: Radar chart showing the dimension level of domain 3 maturity levels from the case study.

Domain 3, shown in Figure 9.11, contains two of the overall weakest dimensions in terms of their combined capability and interoperability maturity levels (criterion 2), D3.1.1: ICT hardware, and D3.1.3: Development and maintenance. With domain 3 consisting of only one subdomain, the subdomain scored amongst the lowest average capability maturity level (criterion 4), as well as below the average subdomain interoperability maturity across all domains (criterion 5).

The practical recommendations with regard to the dimensions in domain three, identified here, are as follows:

Dimension 3.1.1 ICT hardware

The recommendation for this dimension is for the organisation to identify the specific hardware components needed to directly support the processes linked to patient safety. In this case, the organisation has identified cloud-based storage of information as a desirable mechanism to achieve a centralised storage of patient safety information. It was noted that the organisation is dependent on national government to provide a national healthcare technology infrastructure, which is costly. Investment in technological infrastructure may be considered difficult to justify within the healthcare sector because of the perceived lack of tangible benefits on patient health outcomes. However, given the undeniable increase in digital and mobile technology adoption across all industries, these investments should be seen as paramount to ensure digital inclusion of the healthcare sector. It is also important to note that improvements in the healthcare technology infrastructure will not only benefit pharmacovigilance activities, but many other healthcare activities too.

The interoperability of Health Information Technology solutions can only be realised if the HIT solutions are implemented within a core infrastructure of hardware and network connectivity. Hardware infrastructure on an operational level might consist of PCs and mobile devices but the organisation also needs to develop and maintain their data warehousing and storage capabilities. Findings from the PVR-CMM maturity assessment suggest that this would require significant involvement from the government, as the organisation itself has no control over technology capacity at the facility level across the various provinces.

Dimension 3.1.3 Development and maintenance

The successful creation, implementation and acceptance of HIT solutions is largely dependent on workforce engagement and education. Education and training of the end-users is paramount, particularly when it comes to HCPs, it would be advantageous to communicate the benefits of the HIT solution by demonstrating how the HIT directly supports their work practices. Successful use of the HIT solution is dependent on the capabilities of the end-users. Performance capacity is improved with the improvement of personal capacity or skills that enable the effective use of tools, in this case the HIT solution.

It is important to consider the roles of HCPs which use the HIT solutions, as well as the IT workforce who are tasked with designing and developing the HIT solutions. By forming direct linkages between IT and system developers and the end-users, improved functionality and adherence can be achieved. Educating end-users on interoperability and its associated

impacts and benefits through the use of training and educational material, will improve end-user acceptance of newly implemented HIT initiatives. End-users on the operational level of the health system are more likely to accept new HIT initiatives when there is a demonstrable benefit in terms of how the HIT can support their direct needs and work activities. Furthermore, given the continuous advancement of technology, the necessary change management plans must be in place so as to facilitate the inevitable changes that improved technology will bring to the system over time. As technologies and standards evolve over time, interoperability specifications may need to be adapted.

9.5 Validation of PVR-CMM V2

Upon completion of the case study, the final step in determining the applicability, usefulness, and value of the PVR-CMM, is to validate the outcomes of the case study. Recalling from Chapter 8, De Bruin *et al.* (2005) state that the issue of generalisability of maturity models can only be addressed if the maturity model in question is deployed to an entity that is external to the development and verification of the maturity model. In order to formally validate the PVR-CMM, several questions were asked to the national regulatory authority in the case study, as to whether or not the model and its associated methodology could appropriately be used to characterise the organisation's maturity, to the extent that the results and recommended actions are intelligible, and the resulting conclusions from the model's implementation had some degree of utility.

9.5.1 Validation questions

To validate the PVR-CMM V2, a questionnaire was sent to the three case study participants, described in Section 9.3.2. To uphold the integrity of the validation outcomes, the validation questionnaire was sent only to the three participants who were exposed to the entirety of the PVR-CMM V2. The questions included in the validation questionnaire were divided into three groups. The first group of questions refer to the accuracy of the model's ability to characterise the organisation's capability and interoperability maturity levels. These 14 questions, are addressed at a subdomain level (two questions per subdomain, one addressing capability maturity, and the other addressing interoperability maturity), this is because presenting these questions at a dimension level would essentially equate to conducting another maturity assessment altogether. The results of the first group of questions are discussed in Section 9.5.2.

The second group of questions refer to the ability of the PVR-CMM V2 to achieve it's stated aims, as described in Section 7.3. The third and final group of questions refer to the strengths

and weaknesses of the PVR-CMM V2, as well as it's uniqueness and utility. These two groups of questions, together with determining the validity of the PVR-CMM V2, also provide an indication as to whether the PVR-CMM V2 is accepted or rejected by the intended target audience. This refers to the eighth and final phase of Becker *et al.*'s (2009) eight phase procedural model as well as the PVR-CMM phases of development in Table 7.2. The results of the second and third groups of questions are discussed in Section 9.5.2.1.

9.5.2 Validation results

The results of the validation questionnaire are presented here in three groups. Table 9.2, summarises the responses to the 14 questions referring to the ability of the model to accurately reflect the organisation's capability and interoperability maturity levels. Similarly to the questionnaires used in the verification activities in Chapter 8, this validation questionnaire made use of a 5 point Likert scale.

As is evident in Table 9.2, the results of the first 14 questions are overwhelmingly positive. While a response of "unsure" is not necessarily a negative response, the four instances where P1 and P2 answered "unsure" are considered, from a limitations perspective, to be possibly attributable to the effects of response bias. It could be, that due to the participant's roles within the regulatory authority, the participants might have felt as though they were being scrutinised when confronted with a description of their organisation's maturity that they did not consider desirable, similarly to how individuals might feel when being audited, or during performance reviews.

The results in Table 9.2, indicate that the PVR-CMM V2 can accurately characterise the capability and interoperability maturity of an organisation involved in the management of a SRS.

Table 9.2: Summary of case study participant responses in the validation of the PVR-CMM V2 outcomes.

	Validation Questions	P1	P2	P3	Average:
1.1	To what extent do you agree that the results accurately reflect the capability maturity of Subdomain 1: Leadership and Governance?	3	4	5	80,0%
1.2	To what extent do you agree that the results accurately reflect the interoperability maturity of Subdomain 1: Leadership and Governance?	4	3	4	73,3%
2.1	To what extent do you agree that the results accurately reflect the capability maturity of Subdomain 2: Finance and Economics?	4	3	4	73,3%
2.2	To what extent do you agree that the results accurately reflect the interoperability maturity of Subdomain 2: Finance and Economics?	4	3	4	73,3%
3.1	To what extent do you agree that the results accurately reflect the capability maturity of Subdomain 3: Business Objectives?	4	4	4	80,0%
3.2	To what extent do you agree that the results accurately reflect the interoperability maturity of Subdomain 3: Business Objectives?	4	4	4	80,0%
4.1	To what extent do you agree that the results accurately reflect the capability maturity of Subdomain 4: Human Resources?	4	4	5	86,7%
4.2	To what extent do you agree that the results accurately reflect the interoperability maturity of Subdomain 4: Human Resources?	4	4	5	86,7%
5.1	To what extent do you agree that the results accurately reflect the capability maturity of Subdomain 5: Business Procedures?	4	4	4	80,0%
5.2	To what extent do you agree that the results accurately reflect the interoperability maturity of Subdomain 5: Business Procedures?	4	4	4	80,0%
6.1	To what extent do you agree that the results accurately reflect the capability maturity of Subdomain 6: IT Standards?	4	5	4	86,7%
6.2	To what extent do you agree that the results accurately reflect the interoperability maturity of Subdomain 6: IT Standards?	4	5	4	86,7%
7.1	To what extent do you agree that the results accurately reflect the capability maturity of Subdomain 7: IT Infrastructure?	4	5	4	86,7%
7.2	To what extent do you agree that the results accurately reflect the interoperability maturity of Subdomain 7: IT Infrastructure?	4	5	4	86,7%
	Average:	78,6%	81,4%	84,3%	

9.5.2.1 Acceptance/Rejection of the PVR-CMM V2

In order to determine whether the maturity model has been successfully accepted by the target audience, the stated aims of the maturity model must be achieved, from the perspective of the target audience and the context within which the maturity assessment was conducted. This is the eighth and final phase of the PVR-CMM phases of development shown in Table 7.1.

To support the validity of the PVR-CMM V2, as well as to substantiate the overall acceptance of the model, the following questions were directed at the three primary case study participants, the responses from the participants follow each question:

Table 9.3: Summary of case study participant responses in the validation of the PVR-CMM V2 aims.

	Validation Questions	P1	P2	P3
8	Do you have any prior knowledge of pharmacovigilance and spontaneous reporting of ADRs?	Yes	Yes	Yes
9	Do you believe the PVR-CMM can contribute to the improvement of spontaneous reporting systems?	Yes	Yes	Yes
10	Do you believe the PVR-CMM can contribute to the interoperability of spontaneous reporting systems?	Yes	Yes	Yes
11	Do you believe the PVR-CMM can promote and improve interoperability by addressing the degree of integration of systems involved in spontaneous reporting?	Yes	Yes	Yes
12	Do you believe the PVR-CMM can provide guidance on which system components need to be improved?	Yes	Yes	Yes
13	Do you believe the PVR-CMM can provide a means for measuring interoperability progress across the community of spontaneous reporting systems in the global pharmacovigilance landscape?	Yes	Yes	Yes

Question 14: Are you aware of any other approach that has been proposed which is better suited to address the interoperability of spontaneous reporting systems?

In response to question 14, all three of the participants answered no.

Question 15: What do you view as the key strengths of the PVR-CMM?

> "Ability to show progress and feasibility of achieving goals. Ability to relate unit goals to organizational goals."
>
> "Accuracy."
>
> "It is user friendly and easily accessible."

Question 16: What do you view as the key weaknesses of the PVR-CMM?

> "It is more suitable for use at management level as some information the junior staff may not know."
>
> "Lacks flexibility."
>
> "It is time consuming."

The suitability of the PVR-CMM for use at a management level is to be expected, as the model is intended to be used by management and requires information from individuals who have a good understanding of the entire SRS. In terms of the length of time associated with

the maturity assessment, this is also to be expected, as the aim of the tool is to address the maturity of a comprehensive set of dimensions.

Question 17: If the PVR-CMM was to fail in achieving it's stated aim, what would be the reason for this failure?

> "Failure to use it (probably due to ignorance)."
>
> "undefined processes."
>
> "Non implementation of the recommendations."

In response to the case study participant who cited "undefined processes" of the PVR-CMM as the potential reason for failure. This is likely in response to the level of generality in the PVR-CMM and the need to make minor adaptations and refinements to the tool in order to fit the organisation's individual needs. This aspect of the PVR-CMM is addressed in the disclaimer that is included in the introduction to the PVR-CMM V2, as seen in Figure 9.1.

Question 18: Would you recommend the PVR-CMM as a tool to help improve spontaneous reporting systems?

All three of the case study participants indicated that they would recommend the use of the PVR-CMM as a tool to help improve spontaneous reporting systems.

9.5.3 Validation conclusion

Overall, positive feedback was received from all three case study participants. The PVR-CMM V2's ability to achieve its stated aims has been shown to be valid. The strengths of the PVR-CMM V2 reflect the development and design considerations. The case study participants are in agreement that no other tool exists for the purpose of addressing the interoperability of spontaneous reporting systems. The feedback presented in Sections 9.5.2 and 9.5.2.1, suggest the unquestionable acceptance of the PVR-CMM V2.

9.6 Chapter 8: Conclusion

In this chapter the final version of the PVR-CMM was presented. A case study involving the assessment of a SRS operated by an African RA was designed and executed. The results of the assessment were analysed and practical recommendations for improvement were developed. The RA was then asked a series of questions relating to the maturity assessment, to ascertain the extent of the model's generalisability. The response to the validation questions was positive.

Chapter 10

Conclusion

The final chapter contains an overview of the research presented in this dissertation, as well as confirmation that the research objectives, as stated in Section 1.4.2, have been achieved. The limitations of the research are addressed, the contributions of the research are described, and the opportunities and recommendations for further research are discussed.

10.1 Overview of research

The outcome of this research study is a proposed model based on the concept of a CMM, which can be used by MAHs, RAs, or any entity that owns or operates an SRS to measure and assess their PV capabilities in various organisational, informational, and technical, domains and dimensions.

In Chapter 1 the context within which the research problem exists, as well as the aims and objectives of the research were summarised. The research scope and document structure was also described. Chapters 3, 4, 5, and 6, made up the literature review which together informed the development of the PVR-CMM in Chapter 7.

The research methodology of this study was described in Chapter 2. In this chapter, the research philosophy was discussed, as well as the research approach and strategy. The chapter concluded with a discussion on the relevant research tools and techniques which were employed in this dissertation.

The focus of Chapter 3 was to gain an understanding of: the global PV landscape; what is meant by a standardised and interoperable SRS; and the challenges and barriers which affect the spontaneous reporting of ADRs. Furthermore, an analysis of the effects of the lack of an interoperable global PV reporting system was presented. From this step, the extent to which standardisation could alleviate these PV challenges was established.

Chapter 4 involved characterising the global PV system by identifying the role players, their responsibilities, and the communication channels between them. This stage of the research also identified and elaborated on best practices for the reporting of ADRs (the ICH E2B(R3) standard for electronic ICSR transmission), as well as the solutions and services offered by *the* UMC. By understanding the roles and responsibilities of the various role players, the PVR-CMM could be developed with the three perspectives described in Section 7.3 in mind.

In Chapter 5 the concept of an MM was explored and defined within the context of this study. The history of MMs as well as their various types and purposes was explored. The concept of interoperability was also discussed, with a particular focus on the interoperability of HITs in the eHealth field. The chapter concluded with a discussion on the need to take a sociotechnical approach to introducing MMs within an eHealth context.

Taking into consideration the difficulty associated with implementing standardised HITs into large, complex systems, the notion of STSs was investigated in Chapter 6. The PV system was described as a sociotechnical system to gain an improved understanding of how best to design and implement HITs in these complex systems. Through the conceptualisation of the PV system as an STS, the PVR-CMM development process was more cognisant of social, cultural, and political factors, rather than focussing solely on the technological factors.

Drawing on the findings of the preceding literature review chapters, the focus of the dissertation then turned to the development of the PVR-CMM. Chapter 7 detailed the development of the model, based on the concept of a CMM. A procedural model for the development of MMs was followed in this chapter, and the methodology of the PVR-CMM development was laid out.

A body of literature surrounding the interoperability of information systems, as well as health information systems specifically, was studied. From this research, a collection of 18 maturity models and frameworks were identified. A comparison of these 18 models and frameworks assisted with the selection and characterization of the 30 dimensions included in the first generation of the PVR-CMM, which is presented at the end of Chapter 7.

Following the population of the PVR-CMM V1, a verification and validation strategy is described, with the goal of ensuring the PVR-CMM's suitability for implementation in a real world setting. The PVR-CMM V1 was subjected to two verification processes, by engaging with subject matter experts and focussing on the design requirements and model components that made up the PVR-CMM V1. The feedback of the SMEs was incorporated so as to present the final iteration of the PVR-CMM in Chapter 9.

Upon determining the suitability of the PVR-CMM for real-world implementation, the conception of transfer media was described and a case study was designed so as to determine the extent of the PVR-CMM V2's empirical validity. The case study presented in Chapter 9,

involved conducting a maturity assessment of the SRS of an African national pharmaceutical regulatory authority. The results of the assessment were analysed and practical recommendations for improvement were developed. The regulatory authority was then asked a series of questions relating to the maturity assessment, to ascertain the extent of the model's generalisability.

This last chapter contains an overview of the research presented in this dissertation, as well as confirmation that the research objectives, as stated in Section 1.4.2, have been achieved. The limitations of the research are addressed, the contribution of the research is described, and opportunities and recommendations for further research are discussed.

10.2 Achieving the research objectives

It was envisaged that the research objectives (ROs) which would collectively contribute towards achieving the aim stated in Chapter 1 included:

RO1: To conduct a literature review on the structure of the PV landscape and to define concepts and paradigms from this literature relevant to this study.

Chapters 1, 3, and 4, collectively contributed to achieving this research objective, with each chapter progressively contributing more detail towards the understanding of the global PV landscape.

RO2: To evaluate the value of interoperability in the global PV reporting system through a comprehensive and system-based evaluation of the effects of the lack of such interoperability on PV/health outcomes.

This research objective is achieved in Chapter 3 and served as the primary topic of the journal article titled "An investigation into the value of a standardised global pharmacovigilance reporting system". The effects of the lack of interoperability are discussed in Section 3.5 and the potential impacts of interoperability are noted in Section 3.6.

RO3: To identify through a comparative analysis of PV systems, the main elements that such a standardised system would need to comprise of.

Chapter 4 discussed the various role-players and their responsibilities, as well as the communication channels which exist between them. The minimum requirements for an effective PV system, as well as the objectives of PV monitoring systems were described. Chapter 4 also involved a comparison of PV systems in three different contexts, found in Section 4.5.

RO4: To identify barriers to ADR reporting.

Chapters 3, 4, and 6 collectively contribute to the achievement of this research objective. Chapter 3 describes the cultural and economic barriers to ADR reporting. Chapter 4 describes the numerous mechanisms of reporting and the various communication channels between the different role-players in the PV system. Chapter 6 discussed the sociotechnical implications of the poor design and implementation of technology in healthcare systems. The sociotechnical nature of healthcare work is discussed in Section 6.2.1, and a comparison is drawn between a generic sociotechnical system and the PV system, in Section 6.3. Finally, the challenges in PV are related to the failures of sociotechnical systems.

RO5: To conduct a literature review on maturity models with a specific focus on the scientific and design considerations of maturity models; and define concepts and paradigms from this literature that are relevant to this study.

This research objective is addressed in Chapter 5. The history, types, and purposes of MMs was discussed. The concept of maturity models for interoperability was discussed in Section 5.6.2, with a particular focus on the interoperability of HITs in the eHealth field. The chapter concludes with a discussion on the need to include a sociotechnical approach to introducing MMs within an eHealth context, in Section 5.7.

RO6: To conduct a literature review on sociotechnical systems, with a specific focus on the associated theory, and to characterise the PV system as a sociotechnical system.

Chapter 6 addresses this research objective and the PV system is characterised as an STS in Section 6.3. The contents of this chapter contributed towards the international conference proceedings output titled "Sociotechnical considerations for Health Information Technology design and implementation in complex and adaptive health systems". Challenges associated with standardisation in sociotechnical systems are described in Section 6.4, and understanding change in sociotechnical systems is addressed in Section 6.5.2.

RO7: To define the design requirements for a PV reporting capability maturity model.

The design requirements are defined in Section 7.4 of Chapter 7.

RO7.1: To verify the design requirements by engaging subject matter experts.

The design requirements were verified in Section 8.6 of Chapter 8, and additional design requirements were added in Chapter 7 accordingly.

RO8: To search for an existing model which satisfies the design requirements.

Chapter 7 includes a literature review that results in the comparison of 18 MMs, found in Section 7.5. Although none of the MMs from the literature review were able to satisfy all of the design requirements in Section 7.4, the findings from the comparison of the existing models

yielded valuable insights which would guide the development of the PVR-CMM; particularly by informing the selection and classification of the 30 dimensions into the respective domains and subdomains.

RO9: To develop a maturity model for PV reporting activities, rooted in sociotechnical system theory, if such a model does not exist.

Chapter 7 documented the development of the PVR-CMM; which drew from the findings of the four preceding literature review chapters. The inclusion and contents of the 'organisational' and 'informational' domains were influenced by the findings presented in Sections 6.3 and 6.5.

RO9.1: To streamline and refine the maturity model by engaging subject matter experts, with a focus on including an industry perspective, so as to verify that the maturity model is suitable for implementation in a real world setting.

The outcomes of the first and second verification processes described in Sections 8.1 and 8.6, of Chapter 8, resulted in the development of the PVR-CMM V2. At this stage, the model was considered ready for implementation in a real-world setting.

RO10: To design and execute a case study in which the maturity model will be implemented by a key role player in the PV landscape.

The presentation of the PVR-CMM V2, as well as the design and execution of the case study were described in Sections 9.2 and 9.3, of Chapter 9, respectively. The case study was executed with a prominent national pharmaceutical regulatory authority of the SADC region.

RO10.1: To analyse the findings and results of the case study.

The results of the case study, as well as the development of practical recommendations in response to the results, are included in Section 9.4, of Chapter 7.

RO11: To validate the model by determining whether the model can achieve its stated aims, as well as the extent of the model's generalisability.

The validation process was documented in Section 9.5 of Chapter 9. Overall, the results of the validation process were positive and the generalisability of the PVR-CMM V2 was confirmed.

10.3 Limitations

The primary limitation of this study is the time required to take the PVR-CMM through a complete cycle of implementation. This is a common limitation among doctoral studies involving the development of maturity models. An additional limitation faced in this study was the challenge associated with securing the "buy-in" from a national regulatory authority for the case study. Ideally, the PVR-CMM would be subjected to multiple complete implementation

cycles, in various contexts, to evaluate the extent to which the PVR-CMM contributes to the improvement of SRSs, and the interoperability thereof.

A third limitation to this research was the availability of SMEs to engage with during the validation process. It was challenging to find SMEs, involved in PV from a systems perspective, with the required knowledge relating to the functioning of SRSs, the global PV landscape, as well as concepts more often associated with the discipline of engineering, such as interoperability and capability maturity models. During this research endeavour it became clear that PV has received limited attention from the Engineering discipline, however, as stated by SME number three "it is a good concept to apply the CMM to PV activities", thereby alluding to an opportunity for future research efforts.

10.4 Original contribution

This research offers a number of contributions, both practical and theoretical.

10.4.1 Theoretical contribution

During the completion of this dissertation it became clear that PV has received limited attention from the Engineering discipline. As discussed in the research gap in Section 1.3, as well as during the development of the PVR-CMM in Section 7.5; there is no existence of a maturity model which allows for the assessment of spontaneous reporting systems in PV. Therefore, the unique contribution of this research is the PVR-CMM itself. The development of the PVR-CMM is directly relevant to the research gap presented in Section 1.3 of Chapter 1.

An additional theoretical contribution was made in drawing the comparison between pharmacovigilance and a sociotechnical system, as discussed in Chapter 6. The comparison between PV and sociotechnical systems had not been made in the literature. By matching and comparing elements of the PV system with those of sociotechnical systems, a new contribution was made. This contribution is, however, considered a relatively minor natural conclusion which should be true for most systems of this nature.

10.4.2 Practical contribution

Tied to the unique contribution that is the PVR-CMM itself, a practical contribution of this research is the proven practical applicability of the PVR-CMM. This contribution was identified based on the opinions of subject matter experts which were involved in the validation strategy. A significant amount of encouraging feedback was received from the SMEs involved in the verification and validation processes, upon learning about the research in this dissertation. The unique contribution is alluded to by one of the subject matter experts from the first verification

process, whereby they stated that "it is a good concept to apply a capability maturity model to PV activities", implying that they had not encountered a CMM for PV activities in practice. It is evident that pharmacovigilance receives little to no attention from researchers with a systems background. SME 12 stated that the PVR-CMM would be "the best possible starting point in developing a global regulatory authority curriculum in partnership with the WHO".

10.5 Future work

Exploratory research is effective in laying the groundwork that will lead to future studies (Stebbins, 2001). This research endeavour is of value to future research efforts in that a foundation upon which future work can build has been set, potentially saving time and other resources. One of the outcomes of the verification process was the confirmation of value in applying the concept of a CMM to PV activities. As mentioned in Section 10.4.2, the PVR-CMM could potentially be used to assist with the development of a global standardised regulatory authority curriculum, with the WHO.

In terms of the PVR-CMM specifically, improvements for further iterations of the model could include the accompaniment of additional material. The material could include summaries of the PVR-CMM tailored for more specific target audiences, e.g. HCPs, health IT workers, departments and functional groups of MAHs and RAs. By expanding the accompanying material for the PVR-CMM, it is envisioned that further improvements in the accessibility and usability of the PVR-CMM could be achieved.

Longitudinal studies involving the repeated use of the PVR-CMM as well as the continuous monitoring of assessment outcomes and improvement initiatives would contribute significantly to the PVR-CMM's overall validity. The development of key performance indicators for various role players in the PV landscape would contribute to the assessment process.

At the time of this study, it was deemed that wide-spread interoperability in PV as a result of EHR technology is not feasible in the short term, as it is dependent on the large-scale roll-out of EHRs around the world. However, due to the contemporary nature of the research area within which the problem exists, and the constant advancement of technology, EHRs should be re-evaluated continually when conducting research into interoperability in PV.

10.6 Chapter 9: Conclusion

This chapter provided an overview of the research included in this dissertation and the achievement of the research objectives was evaluated. The chapter concludes with a discussion of

the limitations encountered during this research endeavour, as well as the contributions of the research, and the opportunities for future research efforts.

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Appendix A

Chapter 7 supporting content

This appendix provides the supporting content of Chapter 7. The content of this Appendix is as follows:

- Section A.1: PVR-CMM version 1.

A.1 PVR-CMM version 1

Domain	Subdomain	Dimension	Contextual definition
Organisational (pragmatics)	Leadership and governance	Law, regulation, and policy	The existence of the appropriate legal provisions that mandate and guide all PV related activities. Legal requirements and guidelines applicable to all National Competent Authorities/Regulatory Authorities and Marketing Authorisation Holders, regarding the collection, data management and reporting of suspected adverse drug reactions associated with medicinal products for human use.
		Governance structures and commitment	The existence of the appropriate technical, political, and administrative authoritative entities to manage all affairs relating to health information systems. These authoritative entities ensure the optimal functioning of the HIS as well as coordinate stakeholder engagement across all levels of the organisations HIS. Management is actively committed to managing and improving patient safety.
		Business continuity and responsiveness	A business continuity plan seeks to ensure that the necessary business processes can continue to function so as to maintain reporting compliance during times of partial or total system failure. Business continuity is about devising plans and strategies that enable organisations to continue business operations, and enable quick and effective recovery from any type of disruption, whatever its size or cause. Interoperability will not function as intended if the HIS and all its components do not function correctly. Therefore, business continuity of the national HIS is imperative for continuity of strong interoperability services of HIS. This includes putting in place systems for data recovery, continuity of healthcare, continuous flow of funding, staff transition plans, etc. In terms of responsiveness, MAHs are typically legally obligated to submit any and all reported ADRs that they receive within 15 calendar days to the Regulatory Authority which awarded them marketing authorisation.
		Data ethics/ownership	Data ethics addresses the moral dimension of data management. This includes ensuring adherence to ethical principles throughout data generation, recording, curation, processing, dissemination, sharing, and use. Ethical practices should strive to ensure respect for the people behind the data; use of data in accordance with the intentions of the disclosing party; matching privacy and security safeguards to the expectation of individuals and populations from whom data are drawn; and following the law regarding personal health data privacy and security. These practices are sometimes referred to as responsible data practices.
		Monitoring of performance and effectiveness	Processes to monitor the performance and effectiveness of the PV system, including: reviews of the system by those responsible for management, audits, compliance monitoring, inspections, evaluation of the effectiveness of actions taken during improvement initiatives. Attributes from the maturity model to facilitate tracking of inputs, processes, and outputs against desired results of HIS interoperability implementation, and using data to make decisions.
		Transparency and accountability	Communication of patient safety information and safety issues should be coordinated with all stakeholders in PV, while maintaining patient confidentiality. National competent authorities should publicise regular reports on the performance of their PV systems as well as the results of regular system audits. Information used in decision-making processes should be made openly available to ensure objective and collaborative decision-making. Transparency addresses how an organisation is observed by outsiders based on the quality of information that the organisation shares with the public.
		Partnerships	Implementing regulations which detail public-private partnerships specifically for the development of patient safety systems. Regulatory Authorities should clearly communicate the responsibilities and legal requirements of the MAHs within their jurisdiction.
		Stakeholder communication	Establish internal and external communication plans to facilitate the communication within your authority and with external stakeholders at national level.
		Organisational strategy alignment	A shared understanding of the PV operating model within each organisation as well as a clear understanding of each organisations role in the global patient safety system. Implementing best practices and the alignment of operational activities. Organisations must develop clearly defined roles and responsibilities.
		Building a culture of safety	A system of shared actions, values, and beliefs that develop within an organisation and are transferred to new members as the way to perceive, think, and feel in the organisation. Attitudes and behaviours of organisational workforce towards patient safety. Moving from a culture of compliance to a culture of commitment. The key to developing a strong organisational PV culture is to support and manage the natural social and behavioural aspects of the individuals interactions, rather than attempt to force cultural change by decree.
		Organisational change management	Operational processes are clearly linked to performance outcomes and goals. Organisations should seek to embed a culture of continuous improvement.
	Finance and economics	Financial management	Dedicated budget available for PV relate activities. The legal and administrative systems and procedures put in place permitting a government ministry and its agencies and organizations to conduct activities that ensure the correct use of public funds, and which meet defined standards of probity and regularity. Activities include management and control of public expenditures, financial accounting, reporting, and asset management. Proactive investment in technologies which can be leveraged to improve patient safety.
		Financial resource mobilisation	All activities involved in securing new and additional financial resources for an organization (in this case, the HIS). It also involves making better use of and maximising existing financial resources. The existence of any regular financial provisions. Provision of funding demonstrates government commitment to patient safety and can directly improve conditions in the workplace environment which ultimately improves HCPs attitudes towards patient safety.
	Business objectives	Regulatory compliance	All organisations must comply with patient safety reporting requirements which are imposed by the relevant Regulatory Authority. Compliance monitoring policies and strategies. This includes reviews, inspections, and audits which can be conducted regularly internally or by an external actor. A good compliance strategy reduces the risk of business disruption, litigation costs, and reputational damage.
		Resource efficiency and business sustainability	Efficient resource utilisation improves system outputs by maximising the supply of inputs and minimising wasted resource expenses. Resource efficiency means achieving the desired outcomes in a sustainable manner. Business sustainability deals with the ability of an organisation to meet the demands of the present without effecting its ability to meet the demands of the future. Business sustainability typically involves financial, social, and environmental components.
		Data management	Data management consists of the development, execution, and supervision of plans, policies, programs, and practices that control, protect, deliver, and enhance the value of data and information assets for decision making. Data management includes procedures on how data are captured, stored, analysed, transmitted, and packaged for use across the data supply chain.

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Domain	Subdomain	Dimension	Level 0	Capability level 1	Interoperability level 1	Capability level 2
			Incomplete/Absent	Initial	System as silo	Managed
Organisational (pragmatics)	Leadership and governance	Law, regulation, and policy		Some regulations are policies have been developed and implemented, but in an unstructured manner, lacking consistency.	No formal legislation or policies. Any existing policies are localised to the individual system setting. No standardisation,	Legislation has been developed to address patient safety, with a simple but complete set of regulations to support the legislation.
		Governance structures and commitment		No formal governance structures exist and management of HIS affairs occurs on an ad hoc basis.	No formal governance structures. Any existing governance structure is localised to the individual system setting. No standardisation.	Simple, but functional governance structures exist. Governance structures function reactively and unpredictably.
		Business continuity and responsiveness		Initial attempt at developing a business continuity plan has been made, outlining some of the processes needed to ensure business continuity.	No formal business continuity plan is in place across the organisation and any existing business continuity activities are localised to the individual system setting. No standardisation.	Simple, but complete business continuity plan for patient safety activities has been developed.
		Data ethics/ownership		The organisation does not have formal processes or structures in place which address the ethics associated with business processes.	No formal policies for data ethics and ownership. The organisation works without interaction and any arrangements are unplanned and unanticipated. No standardisation.	Simple, but comprehensive set of processes and policy structures in place which address the ethics associated with critical data,
		Monitoring of performance and effectiveness		The organisation is unaware of the performance indicators which it should be measuring. Performance measurement is ad-hoc or by means of external audits and assessments.	Performance monitoring is performed internally with no industry benchmark to make a comparison against. No standardisation.	Simple, but comprehensive set of performance objectives is established. Performance monitoring is performed in a reactive manner.
		Transparency and accountability		Transparency and accountability is not thoroughly understood within the organisation. No comprehensive policy documentation exists addressing transparency and accountability.	Localised understanding of transparency and accountability. No standardisation.	Simple policies addressing transparency and accountability exist. Simple risk management plans associated with accountability exist.
		Partnerships		An initial attempt has been made to identify key partnerships which the organisation should develop.	Partnerships are unplanned and unanticipated, no strategy to manage partnerships exists. No standardisation.	The organisation has established simple partnerships with all organisations that affect its business operations and value creation. The organisation focusses on building confidence in the partnerships.
		Stakeholder communication		No formal communication channels exist within the organisation or between the organisation and its external stakeholders.	No stakeholder communication strategy. Organisation does not interact with any external stakeholders. No standardisation.	Simple communication channels exist both internally and externally.
		Organisational strategy alignment		Business objectives are not well understood by the various departments within the organisation.	Business objectives are developed within the confines of the localised system setting. No standardisation.	Business objectives are understood within departments. Gaps exist between business objectives and business processes.
		Building a culture of safety		Patient safety culture is inconsistently managed. Patient safety is not considered a goal of the organisation.	No formal approach to building a culture of patient safety. No standardisation.	Simple commitment from management to improving patient safety culture within the organisation. Patient safety culture is a culture of compliance.
		Organisational change management		Initial attempt at change management is implemented inconsistently. Recognised need for change management.	Organisational change is not considered a priority as the system is isolated and therefore not influenced by changes in the external environment. No standardisation.	Simple, but effective change management is applied in isolated projects.
	Finance and economics	Financial management		Initial attempt at financial management for patient safety related activities. Recognised need for appropriate financial management.	Financial management strategy is isolated and localised within the confines of the system setting. No standardisation.	Simple, but complete financial management strategy. Finances are managed in an unpredictable and reactive manner.
		Financial resource mobilisation		Funding for patient safety activities is acquired in an unstructured, inconsistent manner.	Financial resource mobilisation strategy is isolated and localised within the confines of the system setting. No standardisation.	Simple, but complete financial resource mobilisation plan.
	Business objectives	Regulatory compliance		The organisation is unaware of the full extent of its compliance obligations. Compliance is assessed ad-hoc or by means of external audits and assessments.	Regulatory compliance is measured in isolation and is localised to the system setting. No standardisation.	The organisations understands the full extent of its compliance obligations. A catalogue of compliance requirements is created. Compliance is managed in an unpredictable and reactive manner.
		Resource efficiency and business sustainability		Ad hoc sustainability policies and practices in place. Resource efficiency not considered a priority.	Resource efficiency and business sustainability activities are isolated and localised to the system setting. No standardisation.	Simple resource efficiency and business sustainability policies and practices are in place. Implemented on a per project basis.
		Data management		Data management is performed ad hoc and inconsistently. A recognised need for formal data management policies and actions.	Data management is confined to the local system setting. No standardisation.	Simple, but complete set of policies and practices addressing the management of data.

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Domain	Subdomain	Dimension	Interoperability level 2	Capability level 3	Interoperability level 3
			Peer-to-peer	Defined	Distributed
Organisational (pragmatics)	Leadership and governance	Law, regulation, and policy	Simple agreements between two homogenous systems are agreed upon to address simple business processes which are shared. Peer-to-peer.	Regulations are tailored to support patient safety activities and policies are developed to ensure compliance.	Legislation is fully distributed across all organisations/role players within the jurisdiction of the National Regulatory Authority. Linking of systems for a common objective.
		Governance structures and commitment	Cooperation of authoritative figures between two systems, governed by simple agreements. Peer-to-peer.	The organisation has a dedicated and committed governance structure which functions proactively to improve patient safety.	Distributed governance structures in place throughout organisation, enabling the organisation to interact with similar organisations in a structured manner.
		Business continuity and responsiveness	Business continuity plans are informally developed between two operating systems based on simple agreements. Peer-to-peer.	Business continuity plan has been implemented and functions in a proactive manner to ensure regulatory compliance.	Business continuity plans include information relating to the functioning of continuity plans across the entire organisation, to avoid disruption of continuity work processes.
		Data ethics/ownership	Interoperability guidelines exist but specific arrangements are unplanned. Simple agreements relating to data ethics and ownership exist between organisations. Work processes linked.	The organisation has a code of ethics and conduct. Individuals are committed to good conduct and strong ethical behaviour.	Interoperability framework in place to address data ethics and ownership. Roles and responsibilities are defined but heterogenous systems are still distinct.
		Monitoring of performance and effectiveness	Performance monitoring is measured against other homogenous systems. Peer-to-peer. Guidelines exist which describe interoperability.	Performance objectives are communicated to the business process owners. Standard procedures for internal performance measurement are developed and conducted on a regular basis.	Streamlining of performance monitoring across the entire organisation according to an interoperability framework. Knowledge is shared.
		Transparency and accountability	Common understanding of transparency and accountability exists between some homogenous organisations. Guidelines exist which describe interoperability.	Transparency and accountability is understood by individuals in the organisation. The organisation has strong policies in place addressing the transparency of their business practices and understands the value of maintaining a positive sentiment by the external environment.	Streamlining of organisational procedures resulting in a common understanding of transparency and accountability between all homogenous organisations exists.
		Partnerships	Guidelines on partnership management are available but specific arrangements are unplanned.	The partnerships are managed and trust is established between partner organisations.	A common partnership management strategy is developed with the help of an organisational interoperability framework. Streamlining or organisational procedures for knowledge sharing.
		Stakeholder communication	Peer-to-peer stakeholder communication based on simple agreements between homogenous organisations. Guidelines exist which describe interoperability.	Well defined communication channels exist within the organisation as well as between the organisation and its external stakeholders.	Stakeholder communication is developed with the help of an organisational interoperability framework. Streamlining or organisational procedures for knowledge sharing.
		Organisational strategy alignment	Work processes and business objectives are linked based on simple agreements in a peer-to-peer manner.	Business objectives are explicitly linked to business processes	Organisational strategy alignment is guided by an organisational interoperability framework. Streamlining or organisational procedures for knowledge sharing.
		Building a culture of safety	Safety culture extends beyond the local setting and is aligned with and linked across homogenous organisations. Guidelines exist which describe interoperability.	Management considers individual societal culture, organisational culture and the interaction between the two. Patient safety culture evolves from a culture of compliance to a culture of commitment.	A culture of patient safety is developed with the help of an organisational interoperability framework. Streamlining or organisational procedures for knowledge sharing.
		Organisational change management	Guidelines on how organisational change management must occur with respect to interoperability. Guidelines exist which describe interoperability.	Comprehensive change management is applied simultaneously over multiple projects within the organisation.	Organisational change is managed with the help of an organisational interoperability framework. Streamlining or organisational procedures for knowledge sharing.
	Finance and economics	Financial management	Financial management activities are linked between homogenous organisations through simple agreements. Guidelines exist which describe interoperability.	Proactive financial management for patient safety related activities. Dedicated budget developed by organisation government to support the achievement of project and organisational performance objectives.	Financial management is guided by an organisational interoperability framework. Streamlining or organisational procedures for knowledge sharing.
		Financial resource mobilisation	Financial resource mobilisation activities are linked between homogenous organisations through simple agreements. Guidelines exist which describe interoperability.	Financial resource mobilisation is tailored to address project and work characteristics. Supports project and organisational performance objectives.	Financial resource mobilisation strategy is guided by an organisational interoperability framework. Streamlining or organisational procedures for knowledge sharing.
	Business objectives	Regulatory compliance	Regulatory compliance work processes are linked between homogenous organisations through simple agreements. Guidelines exist which describe interoperability.	Internal compliance capability development. SOPs and a record management system is in place to manage compliance. Compliance is proactively managed and sustainable.	Regulatory compliance is assessed across homogenous interoperating organisations with the help of an interoperability framework. Streamlining of organisational procedures.
		Resource efficiency and business sustainability	Resource efficiency and business sustainability activities are linked across homogenous organisations through simple agreements. Guidelines exist which describe interoperability.	Proactive efforts across the organisation to improve resource efficiency and business sustainability in all business operations.	Shared knowledge regarding resource efficiency and business sustainability across homogenous organisations which serve a common goal, through streamlining of organisational procedures.
		Data management	Simple agreements regarding data management are implemented allowing simple electronic exchange of data between homogenous systems. Guidelines exist which describe interoperability.	Standard operating procedures are in place for the management of data. A detailed plan of action is developed to migrate from a paper based system to an electronic data management system. The necessary privacy and security measures are included.	Data management is guided by an organisational interoperability framework. Streamlining or organisational procedures for knowledge sharing.

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Domain	Subdomain	Dimension	Capability level 4	Interoperability level 4
			Quantitatively managed	Integrated
Organisational (pragmatics)	Leadership and governance	Law, regulation, and policy	Policies are developed to understand performance variation and detect, refine, or predict the area of focus to achieve quality and process performance objectives associated with patient safety.	National legislation is fully integrated and aligned with international legislation. Policies are harmonised between organisations to share benefits and achieve value interoperability.
		Governance structures and commitment	The organisation has patient safety as a strategic priority which is implemented through a detailed action plan with measurable outcomes.	Governance structure complimentary to other organisations to allow for shared benefits when managing affairs relating to patient safety.
		Business continuity and responsiveness	Business continuity plan is operational and subjected to audits and reviews to ensure the achievement of quality and performance objectives and regulatory compliance.	Business continuity plans include information relating to the interoperability and coexistence with other organisations continuity plans, to avoid disruption of continuity work processes.
		Data ethics/ownership	Individuals within the organisation demonstrate their commitment to the code of ethics and conduct.	Integrated approach to data ethics and ownership across all organisations with shared value systems and goals in the interoperability community.
		Monitoring of performance and effectiveness	The performance and effectiveness of business processes is quantitatively measured both internally and by external audits and assessments.	Integrated performance monitoring. Based on industry benchmarking and external review/assessments between organisations with shared value systems and goals..
		Transparency and accountability	Individuals take responsibility for their work functions and are held accountable for their actions. The organisation monitors the sentiment of outsiders towards their business practices and adapts the business practices accordingly. The organisation has sound risk management plans to assist with accountability.	Integrated understanding of transparency and accountability across heterogenous organisations with shared value systems and goals.
		Partnerships	Service level agreements are agreed upon across partnerships and allow for quantitative measurement.	Partnership management strategies of heterogenous organisations encourage the discovery of new partnership opportunities for different organisations.
		Stakeholder communication	Communication channels are monitored and controlled.	Stakeholder communication activities are linked between heterogenous organisations and interoperability standards are implemented, allowing for the sharing of benefits and value between organisations serving a common goal.
		Organisational strategy alignment	Business processes are adapted to support business objectives and a shared understanding of the linkage between business objectives and business processes is understood within and across organisational departments.	Organisational strategies are linked between heterogenous organisations and interoperability standards are implemented, allowing for the sharing of benefits and value between organisations serving a common goal.
		Building a culture of safety	Leadership uses patient safety outcomes to promote patient safety culture and acts on patient safety improvement initiatives. Visible commitment to patient safety throughout organisation.	Patient safety culture extends and is shared between heterogenous organisations and interoperability standards are implemented, allowing for the sharing of benefits and value between organisations serving a common goal.
		Organisational change management	Organisation makes use of standards and methods for broadly managing and leading change.	Organisational change management activities are linked between heterogenous organisations and interoperability standards are implemented, allowing for the sharing of benefits and value between organisations serving a common goal.
	Finance and economics	Financial management	Finances are quantitatively managed. Expenditures are monitored against budget and finances are subjected to regular audits. Proactive investment in innovation and technology.	Financial management activities are linked between heterogenous organisations and interoperability standards are implemented, allowing for the sharing of benefits and value between organisations serving a common goal.
		Financial resource mobilisation	Financial resource mobilisation has matured to ensure continuous and secure funding for all business processes involved in patient safety.	Financial resource mobilisation activities are linked between heterogenous organisations and interoperability standards are implemented, allowing for the sharing of benefits and value between organisations serving a common goal.
	Business objectives	Regulatory compliance	Internal compliance capabilities are aligned with external auditing and assessment guidelines. The organisation has the capability to predict potentially impactful regulatory changes.	Regulatory compliance activities are linked between heterogenous organisations and interoperability standards are implemented, allowing for the sharing of benefits and value between organisations serving a common goal.
		Resource efficiency and business sustainability	Organisation and business principles are aligned with resource efficiency and business sustainability. Increased profitability is directly associated with resource efficiency and business sustainability.	Resource efficiency and business sustainability activities are linked between heterogenous organisations and interoperability standards are implemented, allowing for the sharing of benefits and value between organisations serving a common goal.
		Data management	Data management processes are disseminated throughout the organisation so as to inform all stakeholders on how their work processes are affected. Data storage and data exchanges are formalised and monitored.	Data management activities are linked between heterogenous organisations and interoperability standards are implemented, allowing for the sharing of benefits and value between organisations serving a common goal.

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Domain	Subdomain	Dimension	Capability level 5	Interoperability level 5
			Optimizing	Universal
Organisational (pragmatics)	Leadership and governance	Law, regulation, and policy	All legislation and policies relating to patient safety are well defined, implemented, and actively reviewed and updated by a wide range of stakeholders.	National legislation is fully integrated and aligned with international legislation. Legislation is continuously updated and improved upon and contributes to the development of the international legislative landscape.
		Governance structures and commitment	Comprehensive and dedicated governance structures in place. Comprising stakeholders from various organisations. Regular reviews and performance measurement of governance structures ensures continuous improvement.	Governance structures are comprised of individuals representing international industry and governments. Continuously reviewed and improved, ultimately contributing to the evolution of the international landscape.
		Business continuity and responsiveness	Regular audits and reviews ensure that the business continuity plan has been fully implemented and ensures the achievement of quality and performance objectives and regulatory compliance.	Business continuity plan is fully integrated with international guidelines, standards and best practices. Continuously reviewed and improved, ultimately contributing to the evolution of the international landscape.
		Data ethics/ownership	The organisation has strong ethical behaviour and a code of ethics and conduct which is aligned with international guidelines and best practices.	A universal approach to data ethics and ownership. All organisations in the global healthcare interoperability community are continually interoperating.
		Monitoring of performance and effectiveness	Quantitative measurement of business performance and effectiveness allows for optimisation of key business processes which contribute significantly to business performance. Performance data provides the capacity to innovate and grow.	Unified performance monitoring. All organisations in the global healthcare interoperability community are continually interoperating.
		Transparency and accountability	The organisation considers transparency and accountability as a value. Communication of auditing and assessment outcomes is done in a transparent manner so as to maintain a positive sentiment by the external environment. Strategic level decision making is inclusive of transparency and accountability principles. The organisation has a robust and agile risk management strategy.	A universal understanding of transparency and accountability across all interoperating organisations in the interoperability community. All organisations in the global healthcare interoperability community are continually interoperating.
		Partnerships	Strong partnerships with partners sharing in value creation, Partnerships are built on a solid foundation of trust and performance with partners seeking mutual benefit across the partnership.	Goal interoperability between among partnerships. Partnerships support the adaptation of work procedures.
		Stakeholder communication	Communication channels are well established. Communication channels within the organisation as well as between the organisation and its external stakeholders are continuously improved.	A universal approach to stakeholder communication. All organisations in the global healthcare interoperability community are continually interoperating. Supporting adaptation and continuous improvement of work procedures.
		Organisational strategy alignment	Strategy development is inclusive of all relevant departments, each of which contributing to support strategy development.	Goal interoperability between all organisations in the global healthcare interoperability community. Universal alignment of organisational strategies regarding patent safety. All organisations in the global healthcare interoperability community are continually interoperating.
		Building a culture of safety	Patient safety culture is firmly rooted in the organisation across all levels and decision making across the health system is patient safety centred. Patient safety is considered an organisational value. Patient safety culture follows a culture of commitment and development.	Patient safety culture is a universal goal of all organisations in the global healthcare interoperability community. All organisations in the global healthcare interoperability community are continually interoperating. Supporting adaptation and continuous improvement of work procedures.
		Organisational change management	Change management is evident across all levels of the organisation and contributes actively to the success of the organisation in meeting its business objectives.	Goal interoperability between all organisations in the global healthcare interoperability community. All organisations in the global healthcare interoperability community are continually interoperating. Supporting adaptation and continuous improvement of work procedures.
	Finance and economics	Financial management	Financial management system is owned, reviewed and actively updated by a wide range of stakeholders.	Goal interoperability between all organisations in the global healthcare interoperability community. All organisations in the global healthcare interoperability community are continually interoperating. Supporting adaptation and continuous improvement of work procedures.
		Financial resource mobilisation	Financial resource mobilisation strategy is owned, reviewed and actively updated by a wide range of stakeholders.	Goal interoperability between all organisations in the global healthcare interoperability community. Universal financial resource mobilisation strategy regarding patent safety. All organisations in the global healthcare interoperability community are continually interoperating. Supporting adaptation and continuous improvement of work procedures.
	Business objectives	Regulatory compliance	Compliance and the associated risks are well understood throughout the organisation and outcomes from compliance processes are used to inform strategic level decision making.	Goal interoperability between all organisations in the global healthcare interoperability community. Universal regulatory compliance regarding patent safety. All organisations in the global healthcare interoperability community are continually interoperating. Supporting adaptation and continuous improvement of work procedures.
		Resource efficiency and business sustainability	Strategic level decision making includes resource efficiency and business sustainability.	Goal interoperability between all organisations in the global healthcare interoperability community. Universal alignment of resource efficiency and business sustainability strategies regarding patent safety. All organisations in the global healthcare interoperability community are continually interoperating.
		Data management	The data management system allows for continuous monitoring of access and use. Electronic data exchange is considered the default method of transferring data both internally and externally. The data management system is continuously improved upon.	Goal interoperability between all organisations in the global healthcare interoperability community. Universal alignment of data management strategies regarding patent safety. All organisations in the global healthcare interoperability community are continually interoperating.

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Domain	Subdomain	Dimension	Contextual definition
Organisational (pragmatics)	Human resources	Human resources policy	The existence of policy documents that specify the roles and responsibilities of the relevant PV staff. Including the designation of a Qualified Person for Pharmacovigilance (QPPV). A set of principles, guidelines, and norms that an organisation adopts to help manage its employees.
		Human resources capacity	Availability of adequate personnel with relevant characteristics, attributes, and capabilities to perform the tasks or sets of tasks outlined by the organisations PV operations and policy documents. This includes people across all stages of the system life cycle, from aspects such as design, development, implementation, and use of the system. (e.g. system architect designers, software developers, implementation and training personnel, as well as HCPs.)
		Human resources capacity development	Awareness, education, and training initiatives aimed at the development of a strong PV culture within the organisation. An organised activity with clear learning outcomes that aims to impart knowledge and skills, shape attitudes, and develop specific competencies and capabilities in personnel. Provision of guidance on the importance of safe practices and procedures for patient safety. Increased sensitisation of healthcare workers on the causes and prevention of adverse events should form part of the continuous professional development of all HCPs. Patient safety training should form part of the curricula of healthcare training institutions.
Informational (Syntax and Semantic)	Business procedures	Data capture	Methods of capturing data associated with the suspected adverse drug reaction. Structured forms, electronic vs paper based, etc.
		Data storage and aggregation	Databases and database management. How data is aggregated for statistical analysis, as well as how duplication errors are avoided.
		Workflows	Workflows describe the necessary sequential steps which need to be taken when performing the business processes. Workflows typically involve the use of Standard Operating Procedures (SOPs). In the context of a spontaneous reporting system this includes receiving the information, case entry, duplicate checking, case registration, case triage, data entry and narrative write up, review, case closure and the transmission of the ICSR.
		Data presentation/ transmission	The format in which data is presented to the subsequent entity in the chain of PV communication.
	IT standards	Data standards	Data standards is inclusive of knowledge representation and terminology standards. Provisions for the inclusion of all relevant structured data useful to assess an individual case. Knowledge representation refers to how medical knowledge is represented within an information system/application context. Collaboration among system users and developers is critical when managing inconsistent knowledge bases. Terminology standards provide specific codes for terminologies and classifications for clinical concepts such as diseases and medications. The terminology systems assign a unique code to a specific disease or entity. An appropriate MedDRA term should be provided in the lowest level term for the drug characterisation along with the resulting suspected adverse reaction. Compliance with standardised medical data content standards such as WHO-ART and MedDRA.
		Information content	The information that is encoded in the ICSR for an ADR report. Standard data elements, provisions for free text narratives. Minimal Information Model for Patient Safety Incident Reporting and Learning Systems. The ICH ICSR E2B (R3) standard, current best practice.
		Data protection, privacy, and security standards	Data protection, privacy and security standards associated with the exchange of patient safety information. Measures to disable unauthorised access of information, manipulation, modification or deletion of information. E.g. The EU General Data Protection Regulation (GDPR).
		Information exchange and interoperability standards	Standards which govern the transmission, organisation and interpretation of electronic data. This includes messaging standards, document standards, application standards, conceptual standards, and architecture standards. These standards are developed by SDOs such as International Standards Organisation (ISO), European Committee for Standardisation (CEN), Health Level Seven (HL7), and OpenEHR.
Technical	IT infrastructure	ICT hardware	The physical hardware needed to support the operation of a spontaneous reporting system. This hardware includes computers, monitors, data input devices/peripherals (mouse, keyboard, etc.), as well as the appropriate cabling and availability of power.
		Network	The existence of the appropriate IT infrastructure to enable the efficient and effective transmission of ICSRs whether it be over local area network (LAN) within a facility or wide area network (WAN) across facilities or organisation in different geographical locations.
		Development and maintenance	Proactive efforts to ensure that the technologies and standards used are maintained and evolved to continually meet the ever changing needs of the system.

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Domain	Subdomain	Dimension	Level 0	Capability level 1	Interoperability level 1	Capability level 2
			Incomplete/Absent	Initial	System as silo	Managed
Organisational (pragmatics)	Human resources	Human resources policy		Roles and responsibilities undefined with work processes being completed inconsistently, on an ad-hoc basis.	No formal interoperability framework addressing human resources policy. HR policy is developed within the confines of the localised system setting. No standardisation.	Simple, but complete set of defined roles and responsibilities with dedicated staff.
		Human resources capacity		Patient safety work processes are performed ad hoc, in an inconsistent manner by unqualified individuals.	HR capacity is managed within the confines of the localised system setting. No standardisation.	Patient safety work processes are identified and assigned to individuals in a structured manner.
		Human resources capacity development		Emerging need for professional development of patient safety workforce. Ad hoc and incidental training occurs by means of mentoring and apprenticeships.	No formal HR capacity development framework in place. HR capacity is developed on an ad hoc basis, unpredictably.	Simple HR capacity development plan in place which targets core competencies.
Informational (Syntax and Semantic)	Business procedures	Data capture		Paper-based system for capturing patient safety information.	Single technology used for data capture. Data capture occurs in an unstructured way and requires manual data integration. No standardisation.	Simple electronic form to capture patient safety information.
		Data storage and aggregation		No electronic database, paper based ADR reports.	Database is designed and developed within the confines of the localised system setting. Data is stored manually. No standardisation.	Simple electronic storage of ADR reports, Microsoft Excel spreadsheet.
		Workflows		Initial attempt at defining workflows has been made but are not comprehensive in nature.	Workflows are developed within the confines of the localised system setting. No standardisation.	Simple, but complete set of patient safety related workflows has been defined.
		Data presentation/ transmission		Paper-based ADR reports mailed via a postal service.	Data transmission is performed manually due to isolated use of technology. No standardisation.	ICSR sent as attachment via e-mail, but not E2B compliant.
	IT standards	Data standards		No formal standards are adhered to, any standards that are adhered to are incidental and on an ad hoc basis.	Data standards are specific to a proprietary system. No interaction between systems negates the need for data standards. No standardisation.	The need for data standards is recognised by the organisation and simple data standards governing the encoding of electronic data are adhered to.
		Information content		No set of minimum information/data elements adhered to. A recognised need for a minimum set of information/data elements.	System as silo means no interaction with other systems and therefore no standard in place for the information content of the ICSR. No standardisation.	The ICSR form has a simple but complete set of basic data elements which constitute the minimum acceptable information.
		Data protection, privacy, and security standards		Identified need for data protection, privacy and security standards. No standards are implemented or adhered to consistently.	System as silo, therefore no data protection, privacy, and security standards are in place. No standardisation.	Some data protection, privacy and security standards are incidentally and unpredictably adhered to.
		Information exchange and interoperability standards		No formal standards are adhered to, any standards that are adhered to are incidental and on an ad hoc basis.	Information exchange and interoperability standards not implemented or adhered to because the system works without interaction with other systems. No standardisation.	The need for interoperability is recognised and simple initiatives are employed to manage interoperability.
Technical	IT infrastructure	ICT hardware		The organisation has inadequate hardware to support patient safety, but is aware of the need for appropriate ICT infrastructure.	Hardware across different operating locations of the organisation is not standardised and does not allow for the exchange of patient safety information. No standardisation.	Simple, but complete assessment of ICT infrastructure needs for supporting patient safety, and a simple but complete infrastructure.
		Network		The organisation has an inadequate network to support the optimal functioning of an information system.	System as silo means that no networking ability is in place and no interaction with other systems in performed. No standardisation.	Simple, but effective IT communications network is operational.
		Development and maintenance		Maintenance and development of the organisations technology infrastructure is performed on an ad hoc basis.	Development and maintenance is localised to the individual system setting. No standardisation.	Simple, but complete set of practices defined to support the development and maintenance of the organisations IT infrastructure.

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Domain	Subdomain	Dimension	Interoperability level 2	Capability level 3	Interoperability level 3
			Peer-to-peer	Defined	Distributed
Organisational (pragmatics)	Human resources	Human resources policy	Guidelines on interoperability exist but specific arrangements relating to human resources policy are unplanned.	Well defined roles and responsibilities with dedicated staff of adequate competency.	Human resources policy is developed according to an organisational interoperability framework, based on organisations with shared goals and common roles and responsibilities.
		Human resources capacity	HR capacity processes of homogenous systems linked and guided by interoperability guidelines.	Standardised roles and responsibilities are entrusted to qualified and capable personnel.	HR capacity is developed with the help of an organisational interoperability framework. Streamlining or organisational procedures for knowledge sharing.
		Human resources capacity development	HR capacity development processes of homogenous organisations linked and guided by interoperability guidelines.	Formal, future-focussed, talent development programs implemented.	HR capacity development strategy is developed with the help of an organisational interoperability framework. Streamlining or organisational procedures for knowledge sharing.
Informational (Syntax and Semantic)	Business procedures	Data capture	Data capture is performed electronically and adheres to standards agreed upon by homogenous systems. Guidelines exist which describe interoperability.	Web-based data capture via a "smart"/interactive form with standard data elements.	Distributed data capture standard. Guided by an interoperability framework. Streamlining of data capture over a central server linking shared logical data models.
		Data storage and aggregation	Database receives and stores data from more than one IT system via simple agreements for simple electronic data exchange, Guidelines exist which describe interoperability.	Dedicated electronic ICSR database is established.	Functional linking of databases which share logical data models across organisations. Standardised safety, security and privacy protocols.
		Workflows	Workflows are partially interoperable with other homogenous systems based on simple agreements for simple data exchange. Guidelines exist which describe interoperability.	Workflows are well defined and standard operating procedures have been developed.	Workflows are linked across facilities of an organisations in the same country and are aligned to achieve a common objective.
		Data presentation/ transmission	Simple electronic data exchange between homogenous systems with discretional pre- and post-exchange data handling. Guidelines exist which describe interoperability.	E2B compliant ICSR sent via e-mail.	Distributed data transmission standard. Streamlining of transmission over a central server linking shared logical data models.
	IT standards	Data standards	Simple data standards are implemented allowing the electronic exchange of data between homogenous systems.	A comprehensive portfolio of data standards is adopted by the organisation. These data standards specifically address all the relevant topics relating to the exchange of electronic healthcare data. Knowledge representation and terminology standards are adhered to.	Distributed portfolio of data standards throughout the organisation. Linking of systems for a common objective. Standardised data protection, security, and privacy protocols in place.
		Information content	Simple agreements between two homogenous systems regarding information content of the ICSR.	Electronic ICSR form with a standard set of data elements. E.g. the Minimal Information Model for Patient Safety (MIM PS). No provision for free text narrative.	Standard information content model developed for the transmission of ICSRs between homogenous systems.
		Data protection, privacy, and security standards	Data protection, privacy, and security standards are based on simple agreements for the simple exchange of electronic data between homogenous organisations.	Specific data protection, privacy and security standards are identified and adhered to.	Data protection, privacy, and security standards are selected and implemented based on an interoperability framework.
		Information exchange and interoperability standards	Information exchange and interoperability standards are implemented allowing the electronic exchange of data between homogenous systems.	Interoperability is understood as a business goal and competitive advantage. Formal interoperability standards are selected and adhered to. Organisational structures are in place to guide interoperability.	Information exchange and interoperability standards are selected and implemented according to an interoperability framework for organisations with shared goals, and aligned roles and responsibilities.
Technical	IT infrastructure	ICT hardware	Hardware at different operating locations of the organisation allows for simple data exchange and the linking of business processes.	The organisation has identified the specific hardware components that directly support the business processes related to patient safety.	Hardware at different operating locations of the organisation allows for linking of business processes which support the common goal of improved patient safety. Safety, security, and privacy standards are implemented.
		Network	Simple agreements regarding LAN capabilities for simple peer-to-peer exchange of electronic data within an organisation.	The organisation has assessed its networking requirements. An implementation plan is in place to improve the efficiency of the IT communications network.	Distributed WAN capability to allow network communication between homogenous systems. Streamlining of organisational procedures. Communication over a central server,
		Development and maintenance	Guidelines for the development and maintenance of the organisations technical infrastructure are available, but are not followed consistently.	Standard operating procedures are in place to manage IT infrastructure development and maintenance to support patient safety business processes.	Development and maintenance of the organisations technical infrastructure is guided by a technology interoperability framework. Streamlining or organisational procedures for knowledge sharing.

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Domain	Subdomain	Dimension	Capability level 4	Interoperability level 4	Capability level 5
			Quantitatively managed	Integrated	Optimizing
Organisational (pragmatics)	Human resources	Human resources policy	Well defined roles and responsibilities with dedicated, fully competent staff, whose performance is measurable with performance indicators/metrics.	Integrated approach to human resources policy development across all heterogenous organisations with shared value systems and goals in the interoperability community.	Performance of human resources is optimal and consistent. Outcomes of quality and process performance objectives are used when reviewing and developing new roles and responsibilities.
		Human resources capacity	Designated staff across all levels of the organisation with the appropriate responsibilities, accountability, and authority for conducting patient safety activities. Patient safety staff are motivated to perform and have a high level of engagement.	HR capacity is sufficient that all heterogenous organisations with shared value systems and goals in the interoperability community are able to share benefits and value.	Patient safety staff take full control over the development of their career and the improvement of their work. Patient safety staff are self-motivating and assist HR with attracting world-class talent.
		Human resources capacity development	A culture of learning and professional development becomes embedded in the organisation. Performance support is available to assist with learning.	HR capacity development is linked across various heterogenous organisations serving a common goal for the sharing of benefits and value.	Continuous professional development. HR capacity development strategy is aligned with business strategy, resulting in an agile and future focussed workforce.
Informational (Syntax and Semantic)	Business procedures	Data capture	Electronic data capture via computer, web portal or mobile application.	Data capture according to international standards to allow interoperability between various heterogenous systems which serve a common goal.	Automated data capture from other information systems (EHRs, pharmacy, labs etc.)
		Data storage and aggregation	ICSR database compatible with medical terminology directories (e.g. MedDRA), access and usage monitoring, validity and duplication detection capability.	Database receives and stores data from multiple heterogenous IT systems. Standardised safety, security and privacy protocols.	ICSR database with backwards and forewords compatibility for the ICH ICSR E2B (R2/R3) standard reporting format.
		Workflows	Quantitative methods are employed to understand performance variation by focussing on process performance objectives.	Workflows from heterogenous organisations which serve a common goal are linked together for shared benefits and value interoperability.	The use of quantitative techniques allow for optimisation and continuous improvement of workflow management and developing and implementing SOPs.
		Data presentation/ transmission	ICSR sent to the UMC via the web-based VigiFlow reporting tool.	Data transmission is according to industry standards, allowing the exchange of data between independent heterogenous systems.	E2B compliant ICSR transmitted via a proprietary gateway application, adhering to the ICH ICSR E2B (R3) business rules for the electronic transmission of ICSRs.
	IT standards	Data standards	The portfolio of data standards has been disseminated throughout the organisation. Compliance is measured by an external auditing body and certification is awarded accordingly.	International standards and best practices adhered to by the organisation, allowing for the integration of heterogenous systems which serve a common goal.	Data standards are regularly reviewed and updated to be consistent with best practices and to ensure interoperability with other health information systems.
		Information content	Electronic ICSR form compliant with the ICH E2B (R3) standard, with a comprehensive set of data elements and the provision for a free text narrative.	Shared information model across various heterogenous systems to allow for transmission of ICSRs within the interoperable community.	A system wherein the sought after information is pulled through on an as requested basis. Through correct harmonisation of systems and standards, information can be requested as opposed to reported or "pushed" to the entity requesting the information. Thus allowing for the inclusion of any and all information available.
		Data protection, privacy, and security standards	Auditing and compliance monitoring of the data protection, privacy and security standards allows for quantitative feedback.	Common data protection, privacy, and security standards are adhered to by various heterogenous organisations which serve a common goal.	Management monitors compliance with data protection, privacy and security standards. Any issues of non-compliance are identified and remedial action is taken to ensure compliance in a timely manner
		Information exchange and interoperability standards	The organisation conducts interoperability compliance assessments to gain insight into which aspects of interoperability require attention. The organisation implements and adheres to a framework for interoperability compliance.	Common information exchange and interoperability standards are implemented across various heterogenous systems, allowing for the sharing of benefits and value between organisations serving a common goal.	The advantages of interoperability are widely understood throughout the organisation and are linked to specific business practices. The organisation leverages these advantages to improve overall efficiency and the bottom line. Information exchange and interoperability standards are regularly reviewed and updated to be consistent with best practices.
Technical	IT infrastructure	ICT hardware	The organisation conducts regular reviews of hardware capabilities and performance to ensure that performance objectives are met.	Hardware across different operating locations of different organisations allows for linking of systems. Integration of heterogenous systems which serve a common goal.	The organisations ICT hardware infrastructure meets international standards. Policies are in place to ensure optimal functioning and maintenance of ICT hardware, allowing for continuous improvement.
		Network	The performance of the organisations IT communication network is measured against performance objectives.	Integrated WAN capabilities enable the integration of heterogenous systems which serve a common goal. Safety, security, and privacy standards are monitored closely.	The organisations IT communications networking capabilities are in line with international standards. Functioning optimally and reliably, and subjected to regular testing and performance reviews.
		Development and maintenance	A dedicated support team takes ownership of the development and maintenance of the organisations IT infrastructure. Proactive development of infrastructure ensures optimal functioning and up-to-date IT infrastructure.	Development and maintenance of technical infrastructure is shared across various heterogenous systems which serve a common goal.	IT infrastructure development and maintenance is focussed on continuous improvement and is performed so as to enable the system to respond to opportunity and change in the future.

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Domain	Subdomain	Dimension	Interoperability level 5
			Universal
Organisational (pragmatics)	Human resources	Human resources policy	A universal approach to human resources policy development. All organisations in the global healthcare interoperability community are continually interoperating. Supporting adaptation and continuous improvement of work procedures.
		Human resources capacity	Continuous improvement in HR capacity ensure continuous interoperation between all organisation in the global healthcare interoperability community. Supporting adaptation and continuous improvement of work procedures.
		Human resources capacity development	HR capacity development is universal and ensures continuous interoperation between all organisation in the global healthcare interoperability community. Supporting adaptation and continuous improvement of work procedures.
Informational (Syntax and Semantic)	Business procedures	Data capture	Data capture standards and applications are fully shared and distributed. All organisations in the global healthcare interoperability community are continually interoperating. Supporting adaptation and continuous improvement of work procedures.
		Data storage and aggregation	Database is fully integrated with international guidelines, standards and best practices. Continuously reviewed and improved, ultimately contributing to the evolution of the global healthcare interoperability community. Supporting adaptation and continuous improvement of work procedures.
		Workflows	Universally agreed upon workflows which support the adaptation and continuous improvement of work procedures. All organisations in the global healthcare interoperability community are continually interoperating.
		Data presentation/ transmission	Data transmission is according to universally agreed upon standards, and can be between any systems in the global healthcare interoperability community. Supporting adaptation and continuous improvement of work procedures.
	IT standards	Data standards	Universally agreed upon and implemented standards which support the adaptation and continuous improvement of work procedures. All organisations in the global healthcare interoperability community are continually interoperating.
		Information content	A common information model is universally distributed allowing the transmission of ICSRs between any organisations in the interoperable community. All organisations in the global healthcare interoperability community are continually interoperating. Supporting adaptation and continuous improvement of work procedures.
		Data protection, privacy, and security standards	Universally agreed upon and implemented data protection, privacy, and security standards which support the adaptation and continuous improvement of work procedures.
		Information exchange and interoperability standards	Universally adopted information exchange and interoperability standards across all organisations participating in the global healthcare interoperability community. All organisations in the global healthcare interoperability community are continually interoperating.
Technical	IT infrastructure	ICT hardware	Hardware allows for complete integration with international guidelines, standards and best practices. Continuously reviewed and improved, ultimately contributing to the evolution of the international landscape. Supporting adaptation and continuous improvement of work procedures.
		Network	Universal communications network established for the exchange of electronic healthcare data. Systems and applications can connect freely and exchange data where permissible, without necessarily serving a common goal. Supporting adaptation and continuous improvement of work procedures.
		Development and maintenance	Universal interoperability of the global health information exchange supports adaptation of work processes relating to the development and maintenance of technical infrastructure.

Appendix B

Chapter 8 supporting content

This appendix provides the supporting content of Chapter 8. The content of this Appendix is as follows:

- Section B.1: PVR-CMM V1 Verification pre-reading document,
- Section B.2: PVR-CMM V1 Verification questionnaire, and
- Section B.3: Responses from subject matter experts.
    - Section B.3.1: Response from SME number one.
    - Section B.3.2: Response from SME number two.
    - Section B.3.3: Response from SME number three.
    - Section B.3.4: Response from SME number four.

B.1 PVR-CMM V1 Verification pre-reading document

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19/10/2018

VALIDATION OF THE PHARMACOVIGILANCE REPORTING CAPABILITY MATURITY MODEL (PVR-CMM)

DOCUMENT 1 OF 2: PRE-READING MATERIAL

PRESENTED BY: MAXIMILLIAN JUAN SCHURER

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1

B. CHAPTER 8 SUPPORTING CONTENT

CONTENTS

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PRE-READING MATERIAL

GLOSSARY

ADR	Adverse drug reaction
EHR	Electronic health record
HCP	Healthcare professional
Heterogenous systems	Two ICT systems which are owned and operated by distinct parent organisations (marketing authorisation holders, or regulatory authorities).
HIT	Health information technology
Homogenous systems	Two ICT systems, potentially in different locations, however, owned and operated by the same parent organisation or regulatory authority.
ICSR	Individual case safety report
ICT	Information and communication technology
Interoperability	The ability of information and communication technology (ICT) systems and the business processes they support to exchange data and to enable the sharing of information and knowledge.
Interoperability community	All organisations or role-players which seek to interoperate in order to receive or give value to and from one another. In this context the interoperability community includes, but is not limited to, regulatory authorities, MAHs, and academia.
MAH	Marketing authorisation holder
PASS	Post authorisation safety study
PSUR	Periodic safety update report
PV	Pharmacovigilance.
PVR-CMM	Pharmacovigilance Reporting Capability Maturity Model
RA	Regulatory authority
Semantic Interoperability	The ability of ICT systems to automatically interpret information exchanged, in a meaningful and accurate manner, to produce useful results as defined by the end user of both systems.
SOP	Standard operating procedure
STS	Sociotechnical system
Syntactic Interoperability	When two or more ICT systems are capable of communicating and exchanging data, through the use of specified data formats and communication protocols.
UMC	Uppsala Monitoring Centre
WHO	World Health Organisation

B. CHAPTER 8 SUPPORTING CONTENT

1. INTRODUCTION

Pharmacovigilance (PV) is based on the medical assessment of adverse medical events or drug-related problems, collected within organised health programmes. The large number of different PV systems, the equally large number of stakeholders within such systems (i.e. pharmaceutical companies, government regulatory bodies, national and international clinical regulatory bodies, healthcare workers, etc.), as well as the significant number of dimensions along which the effectiveness and efficiency could be measured, adds to this complexity. Furthermore, the lack of a standardised reporting protocol across the various PV systems hinders efforts to coherently manage PV on a global scale.

1.1 PROBLEM DEFINITION

The primary obstacle to standardising and achieving interoperability between spontaneous reporting systems globally is the fundamental difference in purpose of the existing spontaneous reporting systems.

The 3 main role-players at the global level of pharmacovigilance are *the* Uppsala Monitoring Centre (the pharmacovigilance working group of the World Health Organisation), the various Marketing Authorisation Holders (MAHs), and the Regulatory Authorities (RAs) representing governments around the world. Each of these three role-players has its own goals and perspectives when conducting PV.

1. *The* UMC: To successfully integrate PV data from all WHO member countries and to perform statistical analysis and continuous monitoring of the global PV landscape.
2. MAHs: To achieve and maintain regulatory compliance, mitigation of financial and market risks, as well as being able to make informed marketing decisions.
3. RAs: To protect and promote patient safety within their public health programs and thus alleviate pressure on their health system.

With this in mind, it is important to note that the strength of the global pharmacovigilance system lies in the integration of various national and industry PV systems. While *the* UMC offers substantial support to the WHO member countries, many of the developing member countries lack the capacity and capability to take full advantage of the services offered by *the* UMC.

1.2 AIM OF THIS STUDY

The aim of this study is to contribute towards the harmonization and interoperability of spontaneous reporting systems in the pharmacovigilance landscape. The development of a maturity model with a sociotechnical system focus will contribute towards this aim – the PVR-CMM (Pharmacovigilance Reporting Capability Maturity Model).

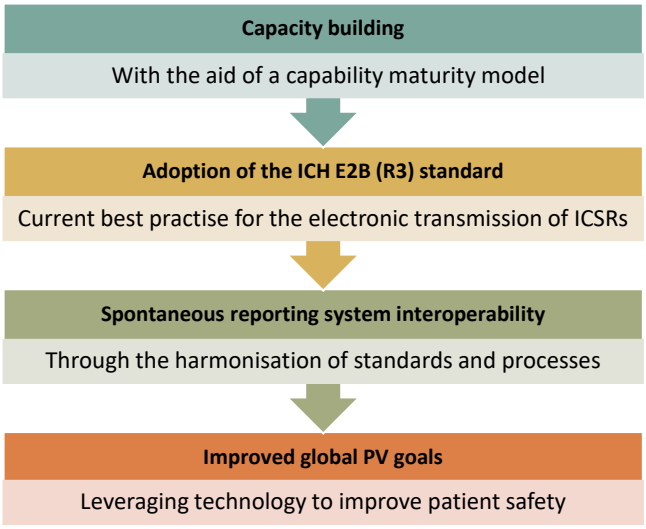

FIGURE 1 SUMMARY OF THE EXPECTED CONTRIBUTION OF THE PVR-CMM.

The PVR-CMM should be useful and of value to MAHs and RAs conducting PV activities by providing guidance on how to reach ICH E2B (R3) compliance and thereby contribute maximally to PV on a global scale, while also receiving maximum value from the services offered by *the* UMC. Figure 1 shows a summary of the expected contribution of the PVR-CMM when used by MAHs or RAs.

1.3 METHODOLOGY OF STUDY

This validation pre-reading document will focus primarily on the PVR-CMM itself, however, key supporting research outcomes and findings will be included in the relevant appendices and referred to where necessary.

The first step in this research was to gain an understanding into the global PV landscape, what is meant by a standardised spontaneous reporting system, the challenges and barriers which affect the spontaneous reporting of adverse drug reactions (ADRs), and an analysis of the effects of the lack of a standardised global PV reporting system. From this step, the extent to which standardisation could alleviate these PV challenges was established.

The next step involved characterising the global PV system by identifying the role-players, their responsibilities, and the communication channels between them. This stage of the research also identifies and elaborates on best practices for the reporting of ADRs (the ICH E2B (R3) standard for electronic Individual Case Safety Report (ICSR) transmission) as well as the solutions and services offered

B. CHAPTER 8 SUPPORTING CONTENT

by *the* UMC. By understanding the roles and responsibilities of the various role-players, the PVR-CMM could be developed with the three perspectives described in section 1.1 in mind.

The use of maturity models as assessment and improvement guidance tools was investigated in the following step in the research. One application of maturity models is to provide guidance towards interoperability. By comparing various maturity models and maturity assessment frameworks in an eHealth context, it was determined that maturity models can also feasibly be used for this purpose within the PV landscape.

Taking into consideration the difficulty associated with implementing standardised health information technologies (HITs) into large, complex systems, the notion of sociotechnical systems was investigated. The pharmacovigilance system was described as a sociotechnical system to gain an improved understanding of how best to design and implement HITs in these complex systems. Further discussion relating to this can be found in Appendix A. Through the conceptualisation of the PV system as a sociotechnical system, the PVR-CMM development process was more cognizant of social, cultural, and political factors, rather than focussing solely on the technological factors.

The concept of the PVR-CMM was then introduced and would be developed using all of the preceding theory and literature findings, from a sociotechnical system perspective.

A body of literature surrounding the interoperability of information systems as well as health information systems specifically was studied. From this research, a collection of 18 maturity models and frameworks were identified. A comparison of these 18 models and frameworks assisted with the selection and characterization of the 30 dimensions included in the PVR-CMM (Appendix B).

1.4 AIM OF VALIDATION PROCESS

The aim of validation process is to engage subject matter experts in the pharmaceutical industry as well as in the regulatory space in order to determine the accuracy, applicability, validity, and value of the PVR-CMM developed in this study. This is achieved by providing each subject matter expert with a brief summary of the research methodology leading up to the development of the PVR-CMM before conducting an interview, guided by a questionnaire.

2. THE PVR-CMM

The PVR-CMM was developed with the intention of being used in conjunction with other PV related statutes, guidelines and documents. The contents of the PVR-CMM should be considered as general guidelines which can be adapted to suit the individual needs of any country or organisation managing a spontaneous reporting system for pharmacovigilance, while incorporating current best practices and achieving and maintaining regulatory compliance.

2.1 STRUCTURE OF THE MODEL

The PVR-CMM is comprised of 3 domains which include 7 subdomains and 30 dimensions. Research suggests that interoperability results as a product of standardisation in four domains: technology, syntax[1], semantics[2], and pragmatics[3].

The PVR-CMM was structured with sociotechnical system engineering principles in mind, that is to say, placing equal importance on the social, political and environmental (workplace) factors. The domains were organised accordingly into three categories: Organisational (pragmatic), Informational (syntax and semantic), and Technical. These three domains lend themselves to the discussion of capability maturity as well as interoperability, and are consistent with the findings of the literature review (Appendix B).

The PVR-CMM further breaks down these three domains and provides subdomains. The subdomains within the organisational domain characterise the pragmatic aspects of interoperability in PV. The informational subdomains characterise the semantics of interoperability, and the technical subdomains emphasise the syntax or format of the information being exchanged between systems.

PV systems involve complex interactions between healthcare professionals, computer hardware and software, as well as the physical work environment within which they operate, all the while being exposed to external pressures from ever changing political, technological, cultural and social factors.

2.2 DIMENSIONS

The 30 dimensions included in the PVR-CMM will be listed below and motivation for their inclusion in the model will be provided. The contextual definition for each of these dimensions is included in the PVR-CMM itself, in the fourth column.

1. Organisational (Pragmatics)

1.1. Leadership & governance

[1] Syntax standardisation refers to the agreement on the structure and language of the message exchanged by heterogenous applications across a network.
[2] Semantic standardisation refers to the extension of syntactic standardisation, that is to say the meaning of the messages are mutually understood.
[3] Pragmatic standardisation refers to agreements on protocols and practices which are prompted by specific messages.

B. CHAPTER 8 SUPPORTING CONTENT

1.1.1. Law, regulation and policy

This dimension serves as acknowledgement of the existence of the appropriate legal provisions that mandate and guide all PV related activities. From an interoperability perspective it is necessary to have a common understanding of legislation relating to the exchange of information and the associated security and privacy issues. Legislation and regulatory guidelines must be compatible and define the boundaries of interoperability between two ICT systems.

1.1.2. Governance structures and commitment

Governance structures are those consisting of the highest executive management of the organisation. The governance structure should enable management to ensure the organisation's compliance with the relevant legislation. Governance impacts change management, regulatory compliance, and also directs the progress of evolving policies and procedures towards interoperability.

1.1.3. Business continuity and responsiveness

Certain pharmacovigilance processes are critical and the appropriate business continuity plans should be developed in a risk-based manner. These processes include collection, processing, management, and timely transmission of ICSRs. Back-up systems allowing exchange of critical information within an organisation, between organisations, or between the MAH and the RA.

1.1.4. Data ethics/ownership

Data ethics addresses the moral dimension of data management. This includes ensuring adherence to ethical principles throughout data generation, recording, curation, processing, dissemination, sharing, and use. With the aim of interoperability being the sharing of data, it is important to stipulate the ownership of the data and to protect and uphold the interests of the owner.

1.1.5. Monitoring of performance and effectiveness

The organisation should clearly define performance indicators which can be used to continuously monitor the performance of PV activities. Monitoring of performance will include activities such as reviews, audits, compliance monitoring, and inspections. Good pharmacovigilance practices have been defined by the European Medicines Agency and can serve as a set of quality requirements for the various PV activities. Corrective and preventative measures can be implemented as a means of addressing performance shortcomings.

1.1.6. Transparency and accountability

Transparency instils trust confidence in the organisation and their system by the public. Accountability refers to the organisation taking responsibility for its actions. Both transparency and accountability are exercised in a PV context through the clear communication of post authorisation safety studies (PASSs) and patient safety update reports (PSURs) by the MAH.

1.1.7.Partnerships

Patient safety and PV activities must be considered when forming and managing partnerships. In the case where multiple partner organisations make use of the same PV system, each partner must ensure that the PV system functions to meet their individual regulatory compliance needs.

1.1.8. Stakeholder communication

Provisions for timely and effective communication of patient safety information or safety concerns to the relevant stakeholders (consumers, HCPs, MAH, RAs, etc.), be it within an organisation or between organisations. This also applies to communication between MAHs and their respective RAs. Coordination and cooperation between the various parties involved in communicating patient safety information, as well as the management of communication tools and channels should seek to improve access to information by those in need of the information.

1.1.9. Organisational strategy alignment

It is important that the organisation has a shared understanding of the PV operating model across all levels of the organisation as well as a common understanding of the role of the organisation within the global patient safety system. Different functional units of an organisation, such as manufacturing, sales and marketing, and quality control, may have contradicting goals and incentive structures, which do not focus on patient safety.

1.1.10. Building a culture of safety

By developing and maintaining a system of shared actions, values, and beliefs, the safety culture will permeate throughout the organisation. A strong culture of safety can help shape the way in which the organisation views PV, from that of a collection of compliance and risk mitigation activities, to a means of developing a set of standard business procedures which yield a competitive advantage.

1.1.11. Organisational change management

Change management processes need to be established to guide the adoption of newly identified best practices and updated work procedures. Change management is critical

B. CHAPTER 8 SUPPORTING CONTENT

when dealing with an ever-changing business environment and the constant introduction of new technologies.

1.2. Finance and Economics

1.2.1. Financial management

A dedicated budget for PV-related activities is crucial. Procedures must be in place to ensure correct spending of funds in the public sector. A proactive approach to investing in innovative technologies must be adopted, e.g. the case of the electronic health record (EHR).

1.2.2. Financial resource mobilisation

Activities relating to the acquisition of new financial resources for the organisation, are vital to guarantee the continued availability of financial resources. These financial resources could include grants, investments from the private sector, or monetary donations from international aid organisations.

1.3. Business Objectives

1.3.1. Regulatory compliance

Organisational policies and processes must always be cognizant of, and remain compliant with, regulatory compliance policies. In order to maintain regulatory compliance, awareness of the applicable legislation and regulations is critical across all stakeholders in the PV system.

1.3.2. Resource efficiency and business sustainability

Business sustainability in this context refers to the organisation's ability to continually control the costs and benefits of interoperability while sustaining the overall quality and performance of their spontaneous reporting system. Achieving efficient utilisation of resources is to exploit system inputs to maximise system outputs, while minimising wasted resources.

1.3.3. Data management

Data management refers to the set of procedures and policies which govern the management of data within the spontaneous reporting system. This includes how data are captured, collected, stored, transmitted and processed.

1.4. Human Resources

1.4.1. Human resources policy

This dimension serves as acknowledgement of the existence of the necessary policies which specify roles and responsibilities for PV in the organisation. Every organisation is legally required to designate a qualified person for pharmacovigilance, this person is tasked with overseeing all PV related activities within the organisation.

1.4.2. Human resources capacity

This refers to the availability of personnel with the relevant and required characteristics, attributes, and capabilities to perform the specified PV roles. PV is a responsibility that is shared across functional business units within an organisation and therefore requires personnel across all stages of the system life cycle.

1.4.3. Human resources capacity development

Awareness, education, and training initiatives aimed at the development of a strong PV culture within the organisation. An organised activity with clear learning outcomes that aims to impart knowledge and skills, shape attitudes, and develop specific competencies and capabilities in personnel.

2. Informational (Syntax and Semantics)

2.1. Business Procedures

2.1.1. Data capture

Methods of capturing data associated with suspected adverse drug reactions and the technologies involved. The WHO states that an ADR reporting form is one of the minimum requirements for a functioning spontaneous reporting system.

2.1.2. Data storage and aggregation

The WHO states that an ADR report database is one of the minimum requirements for a functioning spontaneous reporting system. The methods of aggregating data for statistical analysis, as well as methods for duplicate detection are important when considering the spontaneous reporting system.

2.1.3. Workflows

Workflows detail the sequential steps taken when performing business processes and typically involve standard operating procedures (SOPs).

2.1.4. Data presentation/transmission

The format in which the ICSR is transmitted from the sender to the receiver. Currently the best practice is the ICH E2B (R3) standard for the electronic transmission of ICSRs with backwards/forwards compatibility.

2.2. IT Standards

2.2.1. Data standards

To achieve syntactic interoperability the ICT systems which seek to interoperate must make use of specified data formats and communication protocols.

2.2.2. Information content

The data encoded in an ICSR must collectively represent information that is interpreted in the same way by the ICSR sender and receiver.

2.2.3. Data protection, privacy, and security standards

Information shared by consumers and HCPs has associated rights attributed to the consumers and HCPs, these rights must be protected and respected.

2.2.4. Information exchange and interoperability standards

For interoperability to occur, the interacting ICT systems must agree on the use of standard messaging formats.

3. Technical

3.1. IT Infrastructure

3.1.1. ICT hardware

ICT hardware refers to the physical hardware necessary for the effective and efficient operation of a spontaneous reporting system.

3.1.2. Network

The network refers to the existence of the appropriate IT infrastructure to enable the transmission of ICSRs over a local area network (LAN) or a wide area network (WAN).

3.1.3. Development and maintenance

This dimension refers to the development and maintenance of technologies and standards to ensure optimal performance of the spontaneous reporting system. It is

important to note that maintenance involves different activities at the local and global levels.

2.3 THE TWO MATURITY SCALES

The PVR-CMM makes use of two maturity scales, relating to capability maturity and interoperability maturity respectively. It is believed that by providing two scales according to which maturity can be measured, the PVR-CMM user will better understand how the two perspectives interact with each other.

The capability levels follow the method of the original Capability Maturity Model, developed by the Capability Maturity Model Integration (CMMI) Institute. The term *capability* is associated with specific business processes or a practice area within an organisation. *Maturity* is described as the degree to which an organisation has explicitly and consistently deployed processes, according to their business objectives.

According to the CMMI Institute, the maturity level or capability level of an organisation provides a way to characterise its capability and performance. Organisations should focus their improvement efforts on a prioritised and manageable number of practice areas at a time. Continuous improvement is something which all organisations should seek to embed in their culture. Maturity models assist organisations with linking their business objectives to the improvement goals they seek to achieve. By placing the focus of the organisation on achieving its business objectives with the help of a MM, performance results typically occur naturally and endure for longer.

The CMMI capability levels are as follows (CMMI Institute, 2018):

Level 0: **Incomplete**	Incomplete approach to meeting the intent of the practice area.
Level 1: **Initial**	Initial approach to meeting the intent of the practice area.
Level 2: **Managed**	Subsumes level 1. A simple, but complete set of practices that address the full intent of the practice area.
Level 3: **Defined**	Builds on level 2. Uses organisational standards and tailoring to address project and work characteristics.
Level 4: **Quantitatively Managed**	Builds on level 3. Uses statistical and other quantitative techniques to understand performance variation and detect, refine, or predict the area of focus to achieve quality and performance objectives.
Level 5: **Optimising**	Builds on level 4. Uses statistical and other quantitative techniques to optimise performance and improvement to achieve quality and process performance objectives.

A maturity model which aims to promote and improve interoperability should seek to address the degree of integration of systems involved, provide guidance on which system components need to be improved, as well as provide a means for measuring interoperability progress in a community. Interoperability can be complex when dealing with multiple large systems, it can also be difficult to define because while

B. CHAPTER 8 SUPPORTING CONTENT

interoperability can be measured to some extent, it is not an entity in and of itself. Interoperability can be measured by assessing how diverse entities interact and work together across technical, social, political, and organisational boundaries.

In terms of organisational interoperability, the PVR-CMM was developed with the following levels:

Level 1: **System as silo**	Single technology. No standardisation. Technical and semantic issues are solved.
Level 2: **Peer-to-peer**	Two systems linked for simple exchange of data. Work processes are linked.
Level 3: **Distributed** (Organisation bound; Interorganisational)	Linking of homogenous systems for a common objective. Knowledge is shared.
Level 4: **Integrated** (National; International)	Linking of heterogenous systems for a common goal. Benefits are shared.
Level 5: **Universal**	Systems can connect and disconnect freely and exchange data without serving a common goal.

2.4 CONCLUSION:

This document, in combination with the accompanying questionnaire (document 2 of 2), serves to validate the development of the PVR-CMM. The approach that was followed during the research and development of the PVR-CMM was summarised in this document. Once the validation process is complete, and the feedback from the subject matter experts has been incorporated, the PVR-CMM is deemed valid.

3. REFERENCES:

Braithwaite, J., Runciman, W.B. & Merry, A.F. (2009). Towards safer, better healthcare: harnessing the natural properties of complex sociotechnical systems. Quality and Safety in Health Care, 18, 37-41.

CMMI Institute (2018). Introducing CMMI Development V2.0. https://cmmiinstitute.com/products/cmmi/dev , [Online; accessed 26-07-2018].

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APPENDICES

APPENDIX A

Pharmacovigilance monitoring systems are examples of Health Information Technologies (HITs), a subset of ICTs (Information and communications technologies) which exist within health systems specifically. These PV systems involve complex interactions between healthcare professionals, computer hardware and software, as well as the physical work environment within which they are implemented. Traditional approaches to introduce ICTs into complex systems have been plagued with multiple shortcomings. This has highlighted the need to change the approach to introducing ICTs into such complex healthcare systems.

A sociotechnical system (STS) is one which includes technical systems but also operational processes and people who use and interact with the technical system.

STS engineering places more importance on a user-centred approach; one which focusses more so on job satisfaction and the needs of the end user. The use and value of sociotechnical systems design methods is discussed in more detail in the sociotechnical systems design section of this paper. As with systems engineering and its focus on the end user, the activities related to PV are patient centred.

Pharmacovigilance can be classified as an open sociotechnical system, healthcare professionals interact with hardware and software infrastructure, recording, storing, and sharing data through the use of a human computer interface. These actions coupled with the multidisciplinary nature of communication and workflows in healthcare, influence internal organisational policies and culture, while adapting to ever changing external environments such as rules and regulations (Sittig and Singh, 2010).

The aim of this chapter was to provide an argument for the adoption of sociotechnical systems design approaches to improve the design, implementation, and adoption of health information systems which seek to assist in promoting safer, better healthcare. The need to incorporate the social sciences in the improvement of health information systems has been widely acknowledged in literature (Braithwaite *et al.*, 2009)., however, it has not yet been realised through the application of conventional system design methods in the context of pharmacovigilance.

Large complex systems fail not because of technical inadequacy, but rather because they do not recognise the social and organisational complexity of the environment in which they are implemented.

PV systems involve complex interactions between healthcare professionals, computer hardware and software, as well as the physical work environment within which they operate, all the while being exposed to external pressures from ever changing political, technological, cultural and social factors.

From the findings presented in this research we show that HIT innovations can never be fully achieved with technological advances alone. Problems regarding HIT implementations cannot be solved simply with more or better HIT, improved training of HCPs and better technical support.

The scope of this research revolves around the first stage of the PV system, that is, the reporting of ADRs, and the subsequent propagation of the generated signal to the VigiBase monitoring system of the World Health Organisation. With this in mind, the four levels in Figure 2 will be explained briefly below:

B. CHAPTER 8 SUPPORTING CONTENT

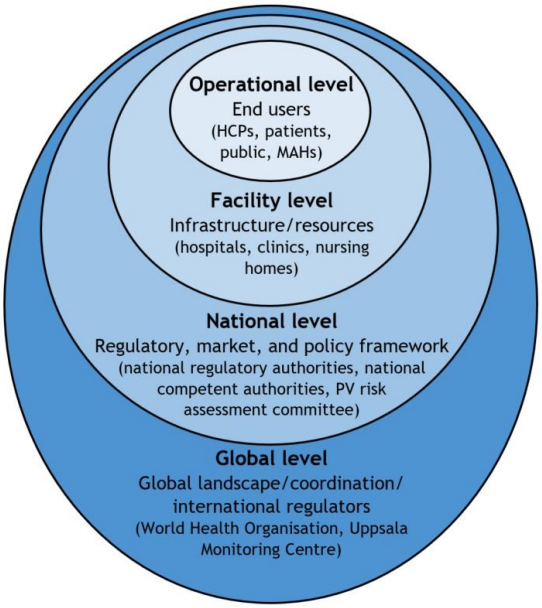

FIGURE 2: A CONCEPTUAL DIAGRAM OF A FOUR-LEVEL HEALTH SYSTEM. (ADAPTED FROM: FERLIE ET AL., 2001)

i. **Operational Level:** From an engineering perspective, the operational level of a system is the level at which decisions relating to the day to day activities of an organisation are made. Spontaneous reporting of suspected ADRs is the cornerstone of pharmacovigilance in that it generates the largest amount of data. It is at the operational level where the HCPs and patients have a direct interaction with the HIT system. At this level the nature of healthcare work and the individual characteristics of the HCPs, such as the knowledge base, skill level, training and education, attitudes, beliefs, and physical capabilities have the largest influence on the success or failure of the system.

ii. **Facility Level:** The facility level encompasses the operational level. The facility within which the HCP works will have a number of intrinsic characteristics, such as the physical environment and layout, the organisational structure, embedded human-system interfaces, communication and coordination practices, as well as local work procedures.

iii. **National Level:** All facility level activities are governed and coordinated at the national level. Each country conducting PV activities will do so according to different healthcare policies, laws and regulations. Decisions made at this level have a trickle-down effect on the facility and operational levels, affecting the overall safety, quality, and efficiency of these parts of the larger system. The PV data generated at the preceding levels is collated and analysed internally by National Competent Authorities before transmitting the signals to the VigiBase system.

iv. **Global Level:** At a global level there are a number of external environmental forces influencing the system, such as technological innovations, economic pressures, political climate, and public awareness. The global level is unique in the context of a PV system in that participatory countries submit their domestic PV data to the World Health Organisation for the benefit of the entire world's population.

Based on these descriptions of the levels of the healthcare system, it becomes clear that the outcome of patient care is produced through the interaction of multiple intricate and fragmented subsystems. This view of a health system highlights the need to educate healthcare providers across all levels and make them aware of their functioning in the greater system that is the healthcare system (Hartman *et al.*, 2017). The successful design and implementation of HITs would therefore be of demonstrable value in terms of improving the delivery of patient care and, in the context of PV, improving patient safety.

To assist with the successful design and implementation of HITs, the notion of a sociotechnical transition must be considered. One must delve into the operational level of the system and consider relationships amongst and between technology and its users across multiple system boundaries. The change process must consider how people work *in situ* rather than merely accept what they 'say they do', as well as how these people translate their beliefs into actions in the workplace and how they make choices in the workplace when executing their power.

B. CHAPTER 8 SUPPORTING CONTENT

APPENDIX B

A body of literature surrounding the interoperability of information systems as well as health information systems specifically was studied. From this research, a collection of 18 maturity models and frameworks were identified. A comparison of these 18 models and frameworks assisted with the selection and characterization of the 30 dimensions included in the PVR-CMM.

See the table below:

Designation	Application Field	Stages/ Levels	Research Method	Components/Influencing factors/Domains/Dimensions	Assessment tool	Reference model	Author	Reference
IT Systems for ADR Reporting: Best Practice Guide	PV	3	Survey, Case studies	ADR IT system functionality: *Collect, Record, Report in E2B, Received ADR data analysis* ADR system maturity level: *Basic, Well developed, Advanced*	n/a	n/a	SCOPE team of the Agency for Medicinal Products and Medical Devices of Croatia (HALMED)	\citep{ADRBP}
Electronic Healthcare Maturity Model (eHMM)	eHealth	7	n/a	Entities, Department, Infrastructure.	n/a	n/a	Quintegra Solutions Limited	\citep{eHMM}
Maturity levels for Interoperability in Digital Government	Interoperability	5	Literature review	Constraints: *Constitutional/legal, Jurisdictional, Collaborative, Organisational, Informational, Managerial, Cost, Technological, Performance.* Maturity levels: *Computer interoperability, Process interoperability, Knowledge interoperability, Value interoperability, Goal interoperability.*	n/a	Stages-of-growth models	Petter Gottschalk, Norwegian School of Management	\citep{gott2009}
GWAC Interoperability Context-Setting Framework	Interoperability	6	Literature review	Interoperability Categories: *Organisational (Economic/Regulatory Policy, Business Objectives, Business Procedures), Informational (Business Context, Semantic Understanding), Technical (Syntactic Interoperability, Network Interoperability, Basic Connectivity).* Cross-cutting Issues: *Configuration and Evolution, Operation and Performance, Security and Safety.* Maturity levels: *0 None, 1 Initial, 2 Managed, 3 Defined, 4 Quantitatively managed, 5 Optimising.*	Yes Evaluation Spreadsheet	CMM	The GridWise Architecture Council	\citep{GWAC}
The Healthcare Analytics Adoption Model (HAAM)	eHealth	9	Observation and Expert opinion	New Data Sources, Complexity, Data Literacy, Data Timeliness.	Yes HAAM Self Inspection Guide	Electronic Medical Record Adoption Model (EMRAM)	Health Catalyst	\citep{HAAM}

19

B. CHAPTER 8 SUPPORTING CONTENT

Designation	Application Field	Stages/ Levels	Research Method	Components/Influencing factors/Domains/Dimensions	Assessment tool	Reference model	Author	Reference
Health Information Systems Interoperability Maturity Model (HISIMM)	eHealth Interoperability	5	Literature review and collaboration with Health Data Collaborative	Domains: *Leadership and Governance, Human Resources, Technology.* Subdomains Maturity levels: *1 Nascent, 2 Emerging, 3 Established, 4 Institutionalised, 5 Optimised.*	Yes	CMM	MEASURE Evaluation and the Health Data Collaborative	\citep{HISIMM}
Maturity Model for Hospital Information Systems (HISMM)	IT Infrastructure	6	Literature review and Survey	Maturity Influencing Factors: *Data analysis, Strategy, People, Electronic medical record, Information security, Systems and IT Infrastructure.*	n/a	Stages-of-growth models	João Vidal Carvalho	\citep{IDCHIT}
Indicator-Based Pharmacovigilance Assessment Tool (IPAT)	PV	n/a	Literature review and Delphi method	Components: (*Policy, Law, and Regulation*), (*Systems, Structures, and Stakeholder Coordination*), (*Signal Generation and Data Management), (Risk Assessment and Evaluation), (Risk Management and Communication).* Indicators: *Core/Supplementary, Structural/Process/Outcome*	Yes	n/a	Strengthening Pharmaceutical Systems	\citep{IPAT}
IT Infrastructure Maturity Model	IT Infrastructure	5	Literature review	Domains: Infrastructure Management, Knowledge, Infrastructure Provisioning, Service Management, Solution Driver, Ecosystem Relationship, Management Focus, Organisation, Agility, Pricing Scheme, Business Interface, Utilisation, Automation and Process Management. Maturity levels: *1 Basic, 2 Controlled, 3 Standardised, 4 Optimised, 5 Innovative.*	Yes	CMM	Ferry Haris, University of Twente	\citep{ITIMM}
Framework for sharing of National eHealth Strategies	eHealth	5	Literature review	Governance: *Leadership and Governance, Strategy and Value Management.* Solutions: *IEHI, Healthcare Service Delivery, Healthcare Information and Knowledge, Public Health and Healthcare Management and Administration.* Foundations and Enablers: *Infrastructure, Standards and Interoperability, IT Process Management, (Legislation, Policy and Compliance), Workforce, Adoption Mechanism, Technological and Innovation*	Yes	CMM	Joint Action to Support the eHealth Network (JASEHN)	\citep{JASEHN}

Designation	Application Field	Stages/ Levels	Research Method	Components/Influencing factors/Domains/Dimensions	Assessment tool	Reference model	Author	Reference
				Trends. Maturity levels: *1 Initial, 2 Ad-hoc, 3 Defined, 4 Managed, 5 Optimised.*				
Pharmacogovernance and Modes of Engagement Model	PV	n/a	Literature review	Policy, Law, Regulation (*Governing structures, Norms, Policy Instruments, Practices, Institutional authority*), Accountability and Transparency, Participation and Representation, Equity and Inclusiveness (*Distribution of resources for PV*), Ethics (*Policy*), Effectiveness and Efficiency (*System integration and communication*), Responsiveness (*Risk communication*), Intelligence and Information (*e-Reporting technology, Risk communication*), Stakeholder communication (*Pooled resources, Network mobilisation, Communication network*).	n/a	n/a	Kathy Moscou, University of Toronto	\citet{KATHY}
National E-Health Transition Authority eHealth Interoperability Framework	eHealth Interoperability	5	Literature review	Interoperability perspectives: *Organisational, Informational, Technical.* Core concepts Patterns	Yes	CMMI	National E-Health Transition Authority of Australia	\citep{NEHTA}
NHS Infrastructure Maturity Model	IT Infrastructure	5	Literature review	Key Capabilities: *Common Applications and Services, Infrastructure Hardware Platforms, Network Devices and Services, IT Security and Information Governance, Infrastructure Patterns and Practices, End User Devices, Infrastructure Governance, Business Alignment, Procurement, People and Skills, Value Management; Principles, Standards, Procedures and Guidelines.* Maturity levels: *1 Basic, 2 Controlled, 3 Standardised, 4 Optimised, 5 Innovative.*	Yes	CMM	Andy Savvides, NHS Connecting for Health	\citep{NIMM}

B. CHAPTER 8 SUPPORTING CONTENT

Designation	Application Field	Stages/ Levels	Research Method	Components/Influencing factors/Domains/Dimensions	Assessment tool	Reference model	Author	Reference
Refined Health European Interoperability Framework (ReEIF)	eHealth Interoperability	n/a	Case studies	Layers of Interoperability: *Legal and Regulatory (legal and regulatory constraints), Policy (collaboration agreements), Care Process (alignment of care processes), Information (defining of coding of information), Applications (integrated healthcare systems), IT Infrastructure (communication protocols).* Implementation levels: *Strategic, Tactical, Operational.* Cross-cutting issues: (*Standards and Profiles, Certification), (Security, Privacy, Governance).*	n/a	n/a	Joint Action to Support the eHealth Network (JASEHN)	\citep{ReEIF}
Telemedicine Service Maturity Model (TMSMM)	eHealth	5	Literature review, Workshops, Case study	Man, Machine, Material, Method, Money.	Yes	CMM	Liezl van Dyk, Stellenbosch University	\citep{vandyk2013}
Healthcare Usability Maturity Model	eHealth	5	Literature review, Case study	Elements: *Focus on Users, Management, Process and Infrastructure, Resources, Education.* Maturity phases: *1 Unrecognised, 2 Preliminary, 3 Implemented, 4 Integrated, 5 Strategic.*	Yes	Various Usability Models	Healthcare Information and Management Systems Society	\citep{UMM}
A Maturity Model for Interoperability in eHealth	eHealth Interoperability	5	Literature review, Case study	Perspectives: *Technical, Procedures, Standardisation.* Maturity levels: *Level 0 (System as silo), Level 1 (Peer-to-peer), Level 2 (Distributed Organisation-bound/Distributed Inter-organisational), Level 3 (Integrated National/Integrated International), Level 5 (Universal).*	n/a	Stages-of-growth models	Lex van Velsen, Telemedicine Cluster Roessingh Research and Development Enschede, the Netherlands	\citep{vanv2016}
WHO Data Collection Tool - Module 11: Pharmacovigilance	PV	n/a	n/a	Legal Underpinnings, Directives, Organisation and Structure, Internal Procedures, Human and Other Resources, Records and Results, Availability of Information.	Yes	n/a	World Health Organization Technical Cooperation for Essential Drugs and Traditional Medicine	\citep{WHODCT}

B.2 PVR-CMM V1 Verification questionnaire

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19/10/2018

VALIDATION OF THE PHARMACOVIGILANCE REPORTING CAPABILITY MATURITY MODEL (PVR-CMM)

DOCUMENT 2 OF 2: QUESTIONNAIRE

PRESENTED BY: MAXIMILLIAN JUAN SCHURER

STELLENBOSCH UNIVERSITY
HEALTH SYSTEMS ENGINEERING & INNOVATION HUB

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Participant Information:

Participant name*: _____

Email address*: _____

Occupation: _____

Industry: _____

*Kindly note that the participant's personal information is required for reference purposes but will not appear in the thesis document or any published document.

2

B. CHAPTER 8 SUPPORTING CONTENT

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QUESTIONS

QUESTION 1: THE PARTICIPANT

1. **ABOUT THE PARTICIPANT** (Please indicate your response with ' **X** ')	**PARTICIPANT'S RESPONSE** **YES**	**NO**
1.1. Are you currently working for an organization which plays a role in the PV system?		
1.2. Are you familiar with the activities relating to Pharmacovigilance?		
1.3. Are you familiar with the national legislation surrounding ADR reporting?		
1.4. Having read the pre-read document, are you familiar with the concept of a capability maturity model?		
1.5. Having read the pre-read document, are you familiar with the concept of interoperability?		

Additional comments:

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QUESTION 2: THE METHODOLOGY

2. The following questions refer to the research methodology (Please indicate your response with ' **X** ')	**Strongly agree** **(4)**	**Agree** **(3)**	**Unsure** **(2)**	**Disagree** **(1)**	**Strongly disagree** **(0)**
2.1. To what extent do you agree that the PVR-CMM has the potential to achieve the stated aim of the study?					

Additional comments:

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4

B. CHAPTER 8 SUPPORTING CONTENT

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QUESTION 3: THE LITERATURE REVIEW

3. **The following questions refer to the literature review** (Please indicate your response with ' **X** ')	**Strongly agree** **(4)**	**Agree** **(3)**	**Unsure** **(2)**	**Disagree** **(1)**	**Strongly disagree** **(0)**
3.1. To what extent do you agree with the finding that the ICH E2B standard is the current best practice for reporting ADRs?					
3.2. To what extent do you agree that the ICH E2B (R3) standard would support harmonization and interoperability of spontaneous reporting systems?					

Additional comments:

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QUESTION 4: THE PVR-CMM FRAMEWORK

4. The following questions refer to the PVR-CMM framework (Please indicate your response with ' **X** ')	**Strongly agree (4)**	**Agree (3)**	**Unsure (2)**	**Disagree (1)**	**Strongly disagree (0)**
4.1. The model represents a comprehensive set of dimensions which characterize the management of a spontaneous reporting system.					
4.2. The PVR-CMM enables the assessment of the maturity of an organization's spontaneous reporting capability.					
4.3. The PVR-CMM can be used to guide improvement initiatives.					
4.4. The PVR-CMM is not bound by application and can be used by a Marketing Authorization Holder as well as a National Regulatory Authority.					
4.5. The PVR-CMM could be used for educational purposes to explain the various aspects of spontaneous reporting to anyone with little or no background in pharmacovigilance.					
4.6. The layout of the PVR-CMM is easy to understand.					
4.7. To what extent do you agree with the domain and subdomain layout of the model?					
4.8. The PVR-CMM achieved its aim of not focusing solely on the technical components of a spontaneous reporting system.					
4.9. The capability and interoperability statements are mutually exclusive.					

6

B. CHAPTER 8 SUPPORTING CONTENT

QUESTION 4: THE PVR-CMM FRAMEWORK

4. **The following questions refer to the PVR-CMM framework** (Please indicate your response with ' **X** ')	**Strongly agree (4)**	**Agree (3)**	**Unsure (2)**	**Disagree (1)**	**Strongly disagree (0)**
4.10. The capability and interoperability statements are collectively exhaustive.					
4.11. The capability statements and maturity levels accumulate while encompassing the preceding statements and maturity levels.					

Additional comments:

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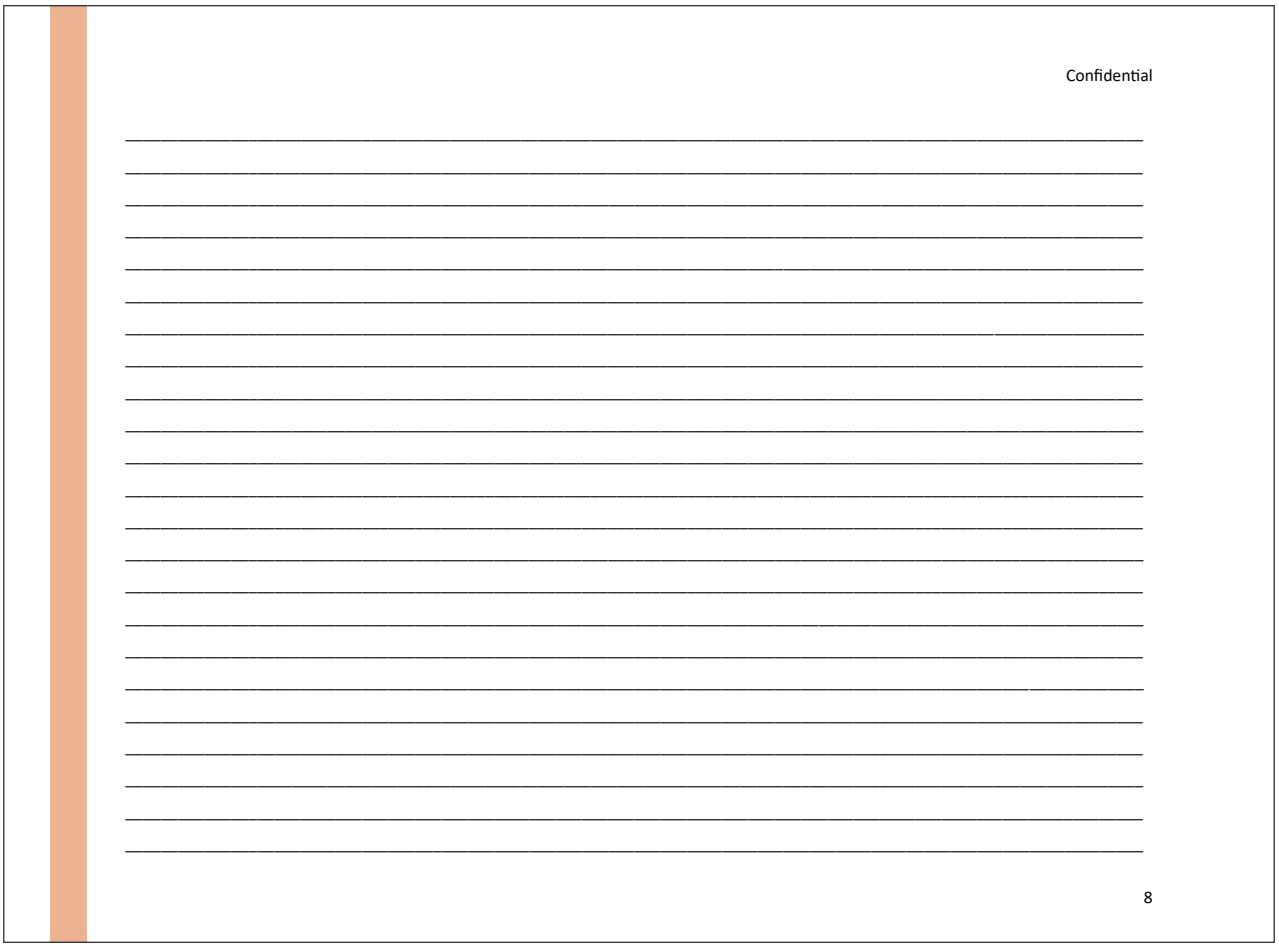

B.3 Responses from subject matter experts

B.3.1 Response from SME number one

Confidential

QUESTIONS

QUESTION 1: THE PARTICIPANT

1. **ABOUT THE PARTICIPANT** (Please indicate your response with '**X**')	**PARTICIPANT'S RESPONSE** YES	NO
1.1. Are you currently working for an organization which plays a role in the PV system?	X	
1.2. Are you familiar with the activities relating to Pharmacovigilance?	X	
1.3. Are you familiar with the national legislation surrounding ADR reporting?		X
1.4. Having read the pre-read document, are you familiar with the concept of a capability maturity model?	X	
1.5. Having read the pre-read document, are you familiar with the concept of interoperability?	X	

Additional comments:

We outsource ADR reporting

3

B. CHAPTER 8 SUPPORTING CONTENT

QUESTION 2: THE METHODOLOGY

2. The following questions refer to the research methodology (Please indicate your response with ' **X** ')	**Strongly agree (4)**	**Agree (3)**	**Unsure (2)**	**Disagree (1)**	**Strongly disagree (0)**
2.1. To what extent do you agree that the PVR-CMM has the potential to achieve the stated aim of the study?		X			

Additional comments:

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QUESTION 3: THE LITERATURE REVIEW

3. The following questions refer to the literature review (Please indicate your response with ' **X** ')	**Strongly agree (4)**	**Agree (3)**	**Unsure (2)**	**Disagree (1)**	**Strongly disagree (0)**

Confidential

QUESTION 3: THE LITERATURE REVIEW

3. **The following questions refer to the literature review** (Please indicate your response with ' **X** ')	**Strongly agree** (4)	**Agree** (3)	**Unsure** (2)	**Disagree** (1)	**Strongly disagree** (0)
3.1. To what extent do you agree with the finding that the ICH E2B standard is the current best practice for reporting ADRs?		X			
3.2. To what extent do you agree that the ICH E2B (R3) standard would support harmonization and interoperability of spontaneous reporting systems?		X			

Additional comments:

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B. CHAPTER 8 SUPPORTING CONTENT

QUESTION 4: THE PVR-CMM FRAMEWORK

4. **The following questions refer to the PVR-CMM framework** (Please indicate your response with ' X ')	**Strongly agree (4)**	**Agree (3)**	**Unsure (2)**	**Disagree (1)**	**Strongly disagree (0)**
4.1. The model represents a comprehensive set of dimensions which characterize the management of a spontaneous reporting system.		X			
4.2. The PVR-CMM enables the assessment of the maturity of an organization's spontaneous reporting capability.	X				
4.3. The PVR-CMM can be used to guide improvement initiatives.	X				
4.4. The PVR-CMM is not bound by application and can be used by a Marketing Authorization Holder as well as a National Regulatory Authority.		X			
4.5. The PVR-CMM could be used for educational purposes to explain the various aspects of spontaneous reporting to anyone with little or no background in pharmacovigilance.			X		
4.6. The layout of the PVR-CMM is easy to understand.		X			
4.7. To what extent do you agree with the domain and subdomain layout of the model?		X			
4.8. The PVR-CMM achieved its aim of not focusing solely on the technical components of a spontaneous reporting system.		X			
4.9. The capability and interoperability statements are mutually exclusive.			X		

Confidential

QUESTION 4: THE PVR-CMM FRAMEWORK

4. **The following questions refer to the PVR-CMM framework** (Please indicate your response with ' X ')	Strongly agree (4)	Agree (3)	Unsure (2)	Disagree (1)	Strongly disagree (0)
4.10. The capability and interoperability statements are collectively exhaustive.			X		
4.11. The capability statements and maturity levels accumulate while encompassing the preceding statements and maturity levels.		X			

Additional comments:

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7

B.3.2 Response from SME number two

Confidential

QUESTIONS

QUESTION 1: THE PARTICIPANT

1. **ABOUT THE PARTICIPANT** (Please indicate your response with '**X**')	**PARTICIPANT'S RESPONSE** YES	NO
1.1. Are you currently working for an organization which plays a role in the PV system?	X	
1.2. Are you familiar with the activities relating to Pharmacovigilance?	X	
1.3. Are you familiar with the national legislation surrounding ADR reporting?	X	
1.4. Having read the pre-read document, are you familiar with the concept of a capability maturity model?	X	
1.5. Having read the pre-read document, are you familiar with the concept of interoperability?	X	

Additional comments:

3

QUESTION 2: THE METHODOLOGY

	Strongly agree	Agree	Unsure	Disagree	Strongly disagree
2. The following questions refer to the research methodology (Please indicate your response with 'X')	**(4)**	**(3)**	**(2)**	**(1)**	**(0)**
2.1. To what extent do you agree that the PVR-CMM has the potential to achieve the stated aim of the study?		X			

Additional comments:

"The aim of this study is to contribute towards the harmonisation of spontaneous reporting systems in the PV landscape".

I think the use of the two maturity scales in the model will well define an organisation's capability/maturity with regard to PV. How this contributes to harmonisation I'm not 100% sure but this is certainly a great first step. Follow-up actions would be required by an organisation to initiate that harmonisation

QUESTION 3: THE LITERATURE REVIEW

3. **The following questions refer to the literature review** (Please indicate your response with '**X**')	**Strongly agree** (4)	**Agree** (3)	**Unsure** (2)	**Disagree** (1)	**Strongly disagree** (0)
3.1. To what extent do you agree with the finding that the ICH E2B standard is the current best practice for reporting ADRs?	X				
3.2. To what extent do you agree that the ICH E2B (R3) standard would support harmonization and interoperability of spontaneous reporting systems?	X				

Additional comments:
No additional comment.

QUESTION 4: THE PVR-CMM FRAMEWORK

4. The following questions refer to the PVR-CMM framework (Please indicate your response with '**X**')	**Strongly agree** (4)	**Agree** (3)	**Unsure** (2)	**Disagree** (1)	**Strongly disagree** (0)
4.1. The model represents a comprehensive set of dimensions which characterize the management of a spontaneous reporting system.	X				
4.2. The PVR-CMM enables the assessment of the maturity of an organization's spontaneous reporting capability.	X				
4.3. The PVR-CMM can be used to guide improvement initiatives.	X				
4.4. The PVR-CMM is not bound by application and can be used by a Marketing Authorization Holder as well as a National Regulatory Authority.		X			
4.5. The PVR-CMM could be used for educational purposes to explain the various aspects of spontaneous reporting to anyone with little or no background in pharmacovigilance.			X		
4.6. The layout of the PVR-CMM is easy to understand.		X			
4.7. To what extent do you agree with the domain and subdomain layout of the model?		X			
4.8. The PVR-CMM achieved its aim of not focusing solely on the technical components of a spontaneous reporting system.	X				
4.9. The capability and interoperability statements are mutually exclusive.			X		

QUESTION 4: THE PVR-CMM FRAMEWORK

4. **The following questions refer to the PVR-CMM framework** (Please indicate your response with '**X**')	**Strongly agree** (4)	**Agree** (3)	**Unsure** (2)	**Disagree** (1)	**Strongly disagree** (0)
4.10. The capability and interoperability statements are collectively exhaustive.		X			
4.11. The capability statements and maturity levels accumulate while encompassing the preceding statements and maturity levels.		X			

Additional comments:

Well thought out and put together, the only reason I haven't strongly agreed with the above statements is because of the length of time it would take me to go through each dimension and scale.

Nevertheless impressive in the time I have. Well done.

B.3.3 Response from SME number three

Confidential

QUESTIONS

QUESTION 1: THE PARTICIPANT

1. **ABOUT THE PARTICIPANT** (Please indicate your response with 'X')	PARTICIPANT'S RESPONSE YES	NO
1.1. Are you currently working for an organization which plays a role in the PV system?	✓	
1.2. Are you familiar with the activities relating to Pharmacovigilance?	✓	
1.3. Are you familiar with the national legislation surrounding ADR reporting?	✓	
1.4. Having read the pre-read document, are you familiar with the concept of a capability maturity model?	✓	
1.5. Having read the pre-read document, are you familiar with the concept of interoperability?	✓	

Additional comments:

3

B. CHAPTER 8 SUPPORTING CONTENT

Confidential

QUESTION 2: THE METHODOLOGY

2. **The following questions refer to the research methodology** (Please indicate your response with 'X')	Strongly agree (4)	Agree (3)	Unsure (2)	Disagree (1)	Strongly disagree (0)
2.1. To what extent do you agree that the PVR-CMM has the potential to achieve the stated aim of the study?		✓			

Additional comments:

4

QUESTION 3: THE LITERATURE REVIEW

	Strongly agree	Agree	Unsure	Disagree	Strongly disagree
3. The following questions refer to the literature review (Please indicate your response with 'X')	(4)	(3)	(2)	(1)	(0)
3.1. To what extent do you agree with the finding that the ICH E2B standard is the current best practice for reporting ADRs?		✓			
3.2. To what extent do you agree that the ICH E2B (R3) standard would support harmonization and interoperability of spontaneous reporting systems?		✓			

Additional comments:

Guidelines aim to improve interoperability and harmonization and I agree that the R3 has achieved this end, however we also need to be cognizant regarding the teething issues in implementation of the R3 vs R2 ? This includes compliance, system upgrades etc.

B. CHAPTER 8 SUPPORTING CONTENT

Confidential

QUESTION 4: THE PVR-CMM FRAMEWORK

	Strongly agree	Agree	Unsure	Disagree	Strongly disagree
4. The following questions refer to the PVR-CMM framework (Please indicate your response with 'X')	(4)	(3)	(2)	(1)	(0)
4.1. The model represents a comprehensive set of dimensions which characterize the management of a spontaneous reporting system.		✓			
4.2. The PVR-CMM enables the assessment of the maturity of an organization's spontaneous reporting capability.		✓			
4.3. The PVR-CMM can be used to guide improvement initiatives.		✓			
4.4. The PVR-CMM is not bound by application and can be used by a Marketing Authorization Holder as well as a National Regulatory Authority.		✓			
4.5. The PVR-CMM could be used for educational purposes to explain the various aspects of spontaneous reporting to anyone with little or no background in pharmacovigilance.		✓			
4.6. The layout of the PVR-CMM is easy to understand.		✓			
4.7. To what extent do you agree with the domain and subdomain layout of the model?		✓			
4.8. The PVR-CMM achieved its aim of not focusing solely on the technical components of a spontaneous reporting system.		✓			
4.9. The capability and interoperability statements are mutually exclusive.		✓			

6

QUESTION 4: THE PVR-CMM FRAMEWORK

	Strongly agree	Agree	Unsure	Disagree	Strongly disagree
4. The following questions refer to the PVR-CMM framework (Please indicate your response with 'X')	(4)	(3)	(2)	(1)	(0)
4.10. The capability and interoperability statements are collectively exhaustive.		✓			
4.11. The capability statements and maturity levels accumulate while encompassing the preceding statements and maturity levels.		✓			

Additional comments:

It is a good concept to apply the CMM to PV activities. The author developed a clear framework of the processes and levels of maturity. There is good literature review in terms of applicable CMM models in the healthcare domain. I agree that more streamlined and standardized PV activities required and E2B R3 aims to address the standardization and interoperability within the EU . However, this remains a challenge even within an EU context... system changes /training/updating SOP's etc which means more resource /cost to the company in the short medium term. How would the CMM address efficiency and cost effectiveness? Another point would be a consideration of looking at region specific needs versus global vs global. How does global challenges specifically translate into African context? Would same infrastructural globally be applicable, relevant or available in a local African context ?

B.3.4 Response from SME number four

Confidential

QUESTIONS

QUESTION 1: THE PARTICIPANT

1. **ABOUT THE PARTICIPANT** (Please indicate your response with ' **X** ')	PARTICIPANT'S RESPONSE YES	NO
1.1. Are you currently working for an organization which plays a role in the PV system?		X
1.2. Are you familiar with the activities relating to Pharmacovigilance?	X	
1.3. Are you familiar with the national legislation surrounding ADR reporting?	X	
1.4. Having read the pre-read document, are you familiar with the concept of a capability maturity model?	X	
1.5. Having read the pre-read document, are you familiar with the concept of interoperability?	X	

Additional comments:

3

B. CHAPTER 8 SUPPORTING CONTENT

Confidential

QUESTION 2: THE METHODOLOGY

	Strongly agree	Agree	Unsure	Disagree	Strongly disagree
2. The following questions refer to the research methodology (Please indicate your response with 'X')	(4)	(3)	(2)	(1)	(0)
2.1. To what extent do you agree that the PVR-CMM has the potential to achieve the stated aim of the study?		X			

Additional comments:

4

Confidential

QUESTION 3: THE LITERATURE REVIEW

	Strongly agree	Agree	Unsure	Disagree	Strongly disagree
3. The following questions refer to the literature review (Please indicate your response with 'X')	(4)	(3)	(2)	(1)	(0)
3.1. To what extent do you agree with the finding that the ICH E2B standard is the current best practice for reporting ADRs?		X			
3.2. To what extent do you agree that the ICH E2B (R3) standard would support harmonization and interoperability of spontaneous reporting systems?		X			

Additional comments:

5

B. CHAPTER 8 SUPPORTING CONTENT

QUESTION 4: THE PVR-CMM FRAMEWORK

	Strongly agree	Agree	Unsure	Disagree	Strongly disagree
4. The following questions refer to the PVR-CMM framework (Please indicate your response with 'X')	(4)	(3)	(2)	(1)	(0)
4.1. The model represents a comprehensive set of dimensions which characterize the management of a spontaneous reporting system.		X			
4.2. The PVR-CMM enables the assessment of the maturity of an organization's spontaneous reporting capability.		X			
4.3. The PVR-CMM can be used to guide improvement initiatives.		X			
4.4. The PVR-CMM is not bound by application and can be used by a Marketing Authorization Holder as well as a National Regulatory Authority.		X			
4.5. The PVR-CMM could be used for educational purposes to explain the various aspects of spontaneous reporting to anyone with little or no background in pharmacovigilance. •			X		
4.6. The layout of the PVR-CMM is easy to understand.		X			
4.7. To what extent do you agree with the domain and subdomain layout of the model?		X			
4.8. The PVR-CMM achieved its aim of not focusing solely on the technical components of a spontaneous reporting system.		X			
4.9. The capability and interoperability statements are mutually exclusive.		X			

QUESTION 4: THE PVR-CMM FRAMEWORK

4. **The following questions refer to the PVR-CMM framework** (Please indicate your response with 'X')	**Strongly agree** (4)	**Agree** (3)	**Unsure** (2)	**Disagree** (1)	**Strongly disagree** (0)
4.10. The capability and interoperability statements are collectively exhaustive.			X		
4.11. The capability statements and maturity levels accumulate while encompassing the preceding statements and maturity levels.			X		

Additional comments:

Appendix C

Chapter 9 supporting content

This appendix provides the supporting content of Chapter 9. The content of this Appendix is as follows:

- Section C.1: Appendix 1 of the PVR-CMM,
- Section C.2: PVR-CMM Version 2, and
- Section C.3: Letter of request for case study.

C.1 Appendix 1 of the PVR-CMM

Spontaneous reporting systems

Spontaneous reporting of adverse drug reactions (ADRs) involves the unsolicited generation of a signal by a health care professional (HCP) or a patient relating to the suspicion of an ADR. Spontaneous reporting is the cornerstone of data generation in post-marketing drug safety and surveillance. This method is advantageous over active surveillance methods in that it covers a large population of potential reporters, as well as a large profile of drugs, and it allows for the monitoring of a medicine throughout its entire life cycle. Spontaneous reporting during the post-marketing phase generates the majority of drug safety data, even more so than the clinical trials during the drug development process.

What is meant by an interoperable spontaneous reporting system?

An interoperable reporting system is envisioned to comprise of the following characteristics:

- A global system wherein an ADR is reported once, with data of high quality to facilitate causality analysis;
- A transparent system where data is accessible by all stakeholders, this includes public health programs (PHPs), regulatory authorities (RAs), manufacturers, HCPs, patients, and the public at large;
- A system which ensures the confidentiality of patients;
- A system which reduces fragmentation and duplication of data and resources;
- A system which improves resource utilization in resource limited contexts;
- A system which reduces administrative pressure, allowing HCPs to direct their attention to other priorities and give them more time to report ADRs; and
- A system which enables HCPs to make more informed therapeutic decisions and improve patient safety.

What are the objectives of such an interoperable spontaneous reporting system?

- To reduce the frequency and severity of ADRs by widening the scope of pharmacovigilance on a global level;
- To improve causality analysis and risk assessment, allowing HCPs to make more informed therapeutic decisions;
- Enabling quantitative conclusions to be made regarding the safety of medicines over long term use; and
- To improve the communication of drug safety information between HCPs and patients.

C. CHAPTER 9 SUPPORTING CONTENT

The successful operation of a spontaneous reporting system is dependent on the successful communication of relevant ADR information from the patient experiencing the ADR to the relevant PV authority, so that the necessary action can be taken so as to prevent medicine related problems and reduce morbidity and mortality associated with ADRs. Reporting or the detection of ADRs and subsequent generation of ADR data is therefore a critical function in the PV system. There exist a multitude of communication channels which are involved during the reporting of ADRs.

In the event of a patient experiencing an ADR from the consumption of a medicine, the reporting process can be initiated in one of two ways, by consulting with a relevant HCP (typically a doctor, a pharmacist or a nurse) or, depending on where the patient lives and the severity of the ADR, direct patient reporting to a regional or national PV centre. The patient and their HCP discuss the ADR and investigate possible causes of the ADR. These causes can include a misdiagnosis, an interaction between the prescribed medicine and another medicine or food substance, an error relating to the administration of the medicine or failure to adhere to the dosing and scheduling instructions of the medicine, or the possibility of the medicine being counterfeit or of sub-standard quality. A decision is reached by the patient and the HCP in terms of how to proceed with the treatment of the ADR, this could include a change in medication, a change in dosage or a change in frequency. This decision is often reached through the collaborative decision-making efforts of multiple healthcare professionals, each with unique knowledge bases, across multiple healthcare disciplines. At this point, in an ideal situation, regardless of the severity, duration or outcome of the ADR, the HCP would initiate a spontaneous report of the ADR to the relevant PV authority such as a regional or national PV centre. The PV authority then compiles an individual case safety report (ICSR) containing all of the relevant information regarding the patient, the ADR, and the suspected drug.

The electronic transmission of ICSRs is outlined by the newly developed ICH E2B(R3) message standard. The standard was developed for the expedited exchange of safety information between systems subjected to various national and international rules and regulations. As the ever-increasing demand for world-wide data exchange continues, there has been a shift from paper-based systems to the electronic transmission of ICSRs using the ICH E2B(R3) standard.

Adding to the complexities already faced in the PV landscape, patient safety messages must be transmitted throughout the product life-cycle. Interoperability is of vital importance when it comes to avoiding difficulties in reconciling ICSRs on a global level, which the World Health Organisation seeks to achieve. The ICH standard is the culmination of efforts to standardise reporting in PV. The recently developed ICSR standard, is a testament that standardised solutions do exist in practice but the challenge standing in the way of worldwide system interoperability lies not in developing these standards, but rather in the adoption and implementation of these standards.

C.2 PVR-CMM Version 2

C. CHAPTER 9 SUPPORTING CONTENT

INTRODUCTION

The **Pharmacovigilance Reporting Capability Maturity Model** (PVR-CMM) is a maturity assessment tool which was developed to assist organisations which own or operate a spontaneous reporting system for pharmacovigilance. The aim of the model is to promote and improve interoperability by addressing the degree of integration of systems involved, providing guidance on which system components need to be improved, as well as providing a means for measuring interoperability progress accross the community of spontaneous reporting systems in the global pharmacovigilance landscape.

Spontaneous reporting of adverse drug reactions is widely considered to be the cornerstone of data generation in pharmacovigilance. Pharmacovigilance systems, by nature, are complex. Spontaneous reporting systems are faced with problems such as under-reporting and the communication of incomplete, unrepresentative, and uncontrolled data. The lack of standardisation and interoperability among these systems results in a reduced capability to detect and characterise new adverse drug interactions and reactions.

Maturity models assist organisations with linking their business objectives to the improvement goals they seek to achieve. By using this maturity assessment tool, an organisation can:

- Identify their current maturity level
- Identify a desired maturity level
- Benchmark and/or compare their capability maturity against a community of similar organisations
- Identify specific dimensions where potential improvement can be made
- Develop a roadmap or plan to grow the organisations maturity to the desired level

The development of the PVR-CMM was the culmination of an extensive multidisciplinary literature review covering aspects of pharmacovigilance, sociotechnical systems, interoperability, and maturity models. Through multiple validation processes with subject matter experts, the PVR-CMM has demonstrated value to organisations which own or operate a spontaneous reporting system.

Disclaimer: The PVR-CMM was developed with the intention of being used in conjunction with other PV related statutes, guidelines and documents. The contents of the PVR-CMM should be considered as general guidelines which can be adapted to suit the individual needs of any country or organisation managing a spontaneous reporting system for pharmacovigilance, while incorporating current best practices and achieving and maintaining regulatory compliance. The PVR-CMM lends support to other pharmacovigilance tools such as the WHO Global Benchmarking Tool and the Indicatior Based Pharmacovigilance Assessment Tool.

It is intended that the user of the PVR-CMM has a sufficient understanding of their organisations pharmacovigilance system so that the necessary adaptations and refinements to the tool can be made to fit the organisation's individual needs. The PVR-CMM has been developed to allow for enough generality to be widely applicable to organisations in pharmacovigilance, but also with enough specificity that it is possible to identify potential areas of weakness and strength. It was deemed necessary to simplify certain complex realities, at the sacrifice of accuracy in some cases, however, the best effort was made to avoid a too generic, vague, or too detailed and too complex approach. Although the covered topics are necessarily complex, simplicity in order to improve readability and applicability was paramount, with the intention of developing a tool which can be used to better understand the situation and define focused, specific strategies for improvement.

Finally, the PVR-CMM should by no means be considered perfect or even complete, it is expected that with feedback from users the model can be continuously improved, making it a better, more accurate tool. To send feedback, please see the note at the bottom of this page.

OVERVIEW

The PVR-CMM is developed in such a way that it aims to be easily understood at a high level, with the details of capability maturity and interoperability maturity of the dimensions being addressed as the user delves deeper into the model.

Research suggests that interoperability results as a product of standardisation in four domains: technology, syntax, semantics, and pragmatics. The PVR-CMM is structured with sociotechnical system engineering principles in mind, that is to say, placing equal importance on the social, political, and environmental (workplace) factors. For these reasons, the 30 dimensions of the PVR-CMM (as seen below) are catagorised into 3 domains: Organisational (pragmatic), Informational (syntax and semantic), and Technical; as well as several subdomains.

The 30 dimensions which make up the PVR-CMM were selected from literature and have been subjected to multiple validation processes whereby subject matter experts from various pharmacovigilance organisations judged their inclusion in the model as critical to the success of a spontaneous reporting system in the global pharmacovigilance landscape. Explicitly, the 30 dimensions are:

Domain 1: Organisational

Subdomain 1: Leadership and Governance
1.1.1 Law, Regulation, and Policy
1.1.2 Governance structures and commitment
1.1.3 Business Continuity and Responsiveness
1.1.4 Data ethics/Ownership
1.1.5 Monitoring of performance and effectiveness
1.1.6 Transparency and accountability
1.1.7 Partnerships
1.1.8 Stakeholder communication
1.1.9 Organisational Strategy alignment
1.1.10 Building a culture of Safety
1.1.11 Organisational change management

Subdomain 2: Finance and Economics
1.2.1 Financial management
1.2.2 Financial resource mobilisation

Subdomain 3: Business Objectives
1.3.1 Regulatory Compliance
1.3.2 Resource efficiency and business sustainability
1.3.3 Data management

Subdomain 4: Human Resources
1.4.1 Human resources policy
1.4.2 Human resources capacity
1.4.3 Human resources capacity development

Domain 2: Informational

Subdomain 1: Business Procedures
2.1.1 Data Capture
2.1.2 Data Storage and Aggregation
2.1.3 Workflows
2.1.4 Data Presentation/Transmission

Subdomain 2: IT Standards
2.2.1 Data Standards
2.2.2 Information content
2.2.3 Data protection, privacy, and security standards
2.2.4 Information exchange and interoperability standards

Domain 3: Technical

Subdomain 1: IT Infrastructure
3.1.1 ICT Hardware
3.1.2 Network
3.1.3 Development and Maintenance

The overall maturity level of the system being assessed is represented by the collective maturity levels of these 30 dimensions. The results section of this tool will provide an overview of the maturity levels, as well as some graphical representations of the maturity levels across the various domains and subdomains.

MATURITY LEVELS

Please direct any feedback regarding this tool to:
16497457@sun.ac.za

Results

MJ Schurer, L Louw, L Bam, IH de Kock

C. CHAPTER 9 SUPPORTING CONTENT

Maturity levels

The PVR-CMM makes use of two maturity scales, relating to capability maturity and interoperability maturity respectively. *Capability* is associated with specific business processes or a practice area within an organisation. Whereas, *maturity* is the degree to which an organisation has explicitly and consistently deployed processes, according to the business objectives. Interoperability can be defined as "the ability of different information technology systems and software applications to communicate, exchange data, and use information that has been exchanged".

The capability maturity levels that are used in the PVR-CMM are exactly the same as those originally developed by the well known CMMI Institute (2018):

CAPABILITY MATURITY		
LEVEL	**NAME**	**DESCRIPTION**
1	**Initial**	Initial approach to meeting the intent of the practice area.
2	**Managed**	Subsumes level 1. A simple, but complete set of practices that address the full intent of the practice area.
3	**Defined**	Builds on level 2. Uses organisational standards and tailoring to address project and work characteristics.
4	**Quantitatively Managed**	Builds on level 3. Uses statistical and other quantitative techniques to understand performance variation and detect, refine, or predict the area of focus to achieve quality and performance objectives.
5	**Optimizing**	Builds on level 4. Uses statistical and other quantitative techniques to optimise performance and improvement to achieve quality and process performance objectives.

The interoperability maturity scale used in the PVR-CMM is based on the work of Gottschalk (2009) and van Velsen *et al.* (2016):

INTEROPERABILITY MATURITY		
LEVEL	**NAME**	**DESCRIPTION**
1	**System as silo**	Single technology. No standardisation. Technical and semantic issues are solved.
2	**Peer-to-peer**	Two systems linked for simple exchange of data. Work processes are linked.
3	**Distributed** (Organisation bound, Inter-organisational)	Linking of homogenous systems for a common objective. Knowledge is shared.
4	**Integrated** (National; International)	Linking of heterogenous systems for a common goal. Benefits shared.
5	**Universal**	Systems can connect and disconnect freely and exchange data without serving a common goal.

INSTRUCTIONS

INSTRUCTIONS

1) Complete the user profile form by clicking the link at the bottom of this page labelled "**PROFILE**"

2) When the profile form is complete, click the link at the bottom labelled "**BEGIN ASSESSMENT**"

3) Read the dimension definition and the maturity statements for both the *capability maturity* and the *interoperability maturity* scales

4) Identify which level description most accurately describes the maturity of the dimension in question

(*Please note that the level descriptions are based on generic situations, so "perfect matches" to your specific reality will be rare.*)

5) Click the drop-down list in the red outlined cell to select the level which you have identified

6) The number of the level and the description of the level will update accordingly

7) Click on the green arrow in the top right corner of the window to navigate to the next dimension

8) Repeat steps 3 - 7 until all of the dimensions have been assessed

9) When all of the dimensions have been assessed the top right corner of the screen will display "**RESULTS**", click here.

10) The results will be summarised and graphical representation of the results can be found using the appropriate links on the results page

PROFILE

C. CHAPTER 9 SUPPORTING CONTENT

Note: *This document forms part of a larger project about pharmacovigilance, namely a PhD dissertation titled "Towards the interoperability of spontaneous reporting systems in pharmacovigilance: a maturity model approach with a sociotechnical system focus". © Maximillian Schurer, Louis Louw, Louzanne Bam, Imke de Kock; Department of Industrial Engineering, Stellenbosch University (Stellenbosch, South Africa).*

PROFILE

Respondent details: (*All fields marked * MUST be completed)*

Date of assessment: *	
Name of respondent: *	
Role or position: *	
Department: *	
Organisation: *	
Internal or External assessment: *	

BEGIN ASSESSMENT

How to?

D1.1.1 Law, Regulation, and Policy

The existence of the appropriate legal provisions that mandate and guide all PV related activities. Legal requirements and guidelines applicable to all National Competent Authorities/Regulatory Authorities and Marketing Authorisation Holders, regarding the collection, data management and reporting of suspected adverse drug reactions associated with medicinal products for human use. From an interoperability perspective it is necessary to have a common understanding of legislation relating to the exchange of information and the associated security and privacy issues. Legislation and regulatory guidelines must be compatible and define the boundaries of interoperability between two ICT systems.

CAPABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	INITIAL

LEVEL	NAME	DESCRIPTION
1	Initial	Some regulations are policies have been developed and implemented, but in an unstructured manner, lacking consistency.
2	Managed	Legislation has been developed to address patient safety, with a simple but complete set of regulations to support the legislation.
3	Defined	Regulations are tailored to support patient safety activities and policies are developed to ensure compliance.
4	Quantitatively Managed	Policies are developed to understand performance variation and detect, refine, or predict the area of focus to achieve quality and process performance objectives associated with patient safety.
5	Optimizing	All legislation and policies relating to patient safety are well defined, implemented, and actively reviewed and updated by a wide range of stakeholders.

INTEROPERABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	SYSTEM AS SILO

LEVEL	NAME	DESCRIPTION
1	System as silo	No formal legislation or policies. Any existing policies are localised to the individual system setting. No standardisation.
2	Peer-to-peer	Simple agreements between two homogenous systems are agreed upon to address simple business processes which are shared. Peer-to-peer.
3	Distributed	Legislation is fully distributed across all organisations/role players within the jurisdiction of the National Regulatory Authority. Linking of systems for a common objective.
4	Integrated	National legislation is fully integrated and aligned with international legislation. Policies are harmonised between organisations to share benefits and achieve value interoperability.
5	Universal	National legislation is fully integrated and aligned with international legislation. Legislation is continuously updated and improved upon and contributes to the development of the international legislative landscape.

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Results

D1.1.2 Governance structures and commitment

The existence of the appropriate technical, political, and administrative authoritative entities to manage all affairs relating to health information systems. These authoritative entities ensure the optimal functioning of the HIS as well as coordinate stakeholder engagement across all levels of the organisations HIS. Management is actively committed to managing and improving patient safety. The governance structure should enable management to ensure the organisation's compliance with the relevant legislation. Governance impacts change management, regulatory compliance, and also directs the progress of evolving policies and procedures towards interoperability.

CAPABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	INITIAL

LEVEL	NAME	DESCRIPTION
1	Initial	No formal governance structures exist and management of HIS affairs occurs on an ad hoc basis.
2	Managed	Simple, but functional governance structures exist. Governance structures function reactively and unpredictably.
3	Defined	The organisation has a dedicated and committed governance structure which functions proactively to improve patient safety.
4	Quantitatively Managed	The organisation has patient safety as a strategic priority which is implemented through a detailed action plan with measurable outcomes.
5	Optimizing	Comprehensive and dedicated governance structures in place. Comprising stakeholders from various organisations. Regular reviews and performance measurement of governance structures ensures continuous improvement.

INTEROPERABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	SYSTEM AS SILO

LEVEL	NAME	DESCRIPTION
1	System as silo	No formal legislation or policies. Any existing policies are localised to the individual system setting. No standardisation.
2	Peer-to-peer	Cooperation of authoritative figures between two systems, governed by simple agreements. Peer-to-peer.
3	Distributed	Distributed governance structures in place throughout organisation, enabling the organisation to interact with similar organisations in a structured manner.
4	Integrated	Governance structure complimentary to other organisations to allow for shared benefits when managing affairs relating to patient safety.
5	Universal	Governance structures are comprised of individuals representing international industry and governments. Continuously reviewed and improved, ultimately contributing to the evolution of the international landscape.

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Results

D1.1.3 Business Continuity and Responsiveness

A business continuity plan seeks to ensure that the necessary business processes can continue to function so as to maintain reporting compliance during times of partial or total system failure. Business continuity is about devising plans and strategies that enable organisations to continue business operations, and enable quick and effective recovery from any type of disruption, whatever its size or cause. Certain PV processes are critical and the appropriate business continuity plans should be developed in a risk-based manner. These processes include collection, processing, management, and timely transmission of ICSRs. Back-up systems allowing exchange of critical information within an organisation, between organisations, or between the MAH and the RA. Interoperability will not function as intended if the HIS and all its components do not function correctly. Therefore, business continuity of the national HIS is imperative for continuity of strong interoperability services of HIS. This includes putting in place systems for data recovery, continuity of healthcare, continuous flow of funding, staff transition plans, etc. In terms of responsiveness, MAHs are typically legally obligated to submit any and all reported ADRs that they receive within 15 calendar days to the Regulatory Authority which awarded them marketing authorisation.

CAPABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	INITIAL

LEVEL	NAME	DESCRIPTION
1	Initial	Initial attempt at developing a business continuity plan has been made, outlining some of the processes needed to ensure business continuity.
2	Managed	Simple, but complete business continuity plan for patient safety activities has been developed.
3	Defined	Business continuity plan has been implemented and functions in a proactive manner to ensure regulatory compliance.
4	Quantitatively Managed	Business continuity plan is operational and subjected to audits and reviews to ensure the achievement of quality and performance objectives and regulatory compliance.
5	Optimizing	Regular audits and reviews ensure that the business continuity plan has been fully implemented and ensures the achievement of quality and performance objectives and regulatory compliance.

INTEROPERABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	SYSTEM AS SILO

LEVEL	NAME	DESCRIPTION
1	System as silo	No formal business continuity plan is in place across the organisation and any existing business continuity activities are localised to the individual system setting. No standardisation.
2	Peer-to-peer	Business continuity plans are informally developed between two operating systems based on simple agreements. Peer-to-peer.
3	Distributed	Business continuity plans include information relating to the functioning of continuity plans across the entire organisation, to avoid disruption of continuity work processes.
4	Integrated	Business continuity plans include information relating to the interoperability and coexistence with other organisations continuity plans, to avoid disruption of continuity work processes.
5	Universal	Business continuity plan is fully integrated with international guidelines, standards and best practices. Continuously reviewed and improved, ultimately contributing to the evolution of the international landscape.

D1.1.4 Data ethics/Ownership

Data ethics addresses the moral dimension of data management. This includes ensuring adherence to ethical principles throughout data generation, recording, curation, processing, dissemination, sharing, and use. Ethical practices should strive to ensure respect for the people behind the data; use of data in accordance with the intentions of the disclosing party; matching privacy and security safeguards to the expectation of individuals and populations from whom data are drawn; and following the law regarding personal health data privacy and security. These practices are sometimes referred to as responsible data practices.

CAPABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	INITIAL

LEVEL	NAME	DESCRIPTION
1	Initial	The organisation does not have formal processes or structures in place which address the ethics associated with business processes.
2	Managed	Simple, but comprehensive set of processes and policy structures in place which address the ethics associated with critical data,
3	Defined	The organisation has a code of ethics and conduct. Individuals are committed to good conduct and strong ethical behaviour.
4	Quantitatively Managed	Individuals within the organisation demonstrate their commitment to the code of ethics and conduct.
5	Optimizing	The organisation has strong ethical behaviour and a code of ethics and conduct which is aligned with international guidelines and best practices.

INTEROPERABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	SYSTEM AS SILO

LEVEL	NAME	DESCRIPTION
1	System as silo	No formal policies for data ethics and ownership. The organisation works without interaction and any arrangements are unplanned and unanticipated. No standardisation.
2	Peer-to-peer	Interoperability guidelines exist but specific arrangements are unplanned. Simple agreements relating to data ethics and ownership exist between organisations. Work processes linked.
3	Distributed	Interoperability framework in place to address data ethics and ownership. Roles and responsibilities are defined but heterogenous systems are still distinct.
4	Integrated	Integrated approach to data ethics and ownership across all organisations with shared value systems and goals in the interoperability community.
5	Universal	A universal approach to data ethics and ownership. All organisations in the global healthcare interoperability community are continually interoperating.

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Results

D1.1.5 Monitoring of performance and effectiveness

Processes to monitor the performance and effectiveness of the PV system, including: reviews of the system by those responsible for management, audits, compliance monitoring, inspections, evaluation of the effectiveness of actions taken during improvement initiatives. Attributes from the maturity model to facilitate tracking of inputs, processes, and outputs against desired results of HIS (Health Information System) interoperability implementation, and using data to make decisions. Good PV practices have been defined by the European Medicines Agency and can serve as a set of quality requirements for the various PV activities. Corrective and preventative measures can be implemented as a means of addressing performance shortcomings.

CAPABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	INITIAL

LEVEL	NAME	DESCRIPTION
1	Initial	The organisation is unaware of the performance indicators which it should be measuring. Performance measurement is ad-hoc or by means of external audits and assessments.
2	Managed	Simple, but comprehensive set of performance objectives is established. Performance monitoring is performed in a reactive manner.
3	Defined	Performance objectives are communicated to the business process owners. Standard procedures for internal performance measurement are developed and conducted on a regular basis.
4	Quantitatively Managed	The performance and effectiveness of business processes is quantitatively measured both internally and by external audits and assessments.
5	Optimizing	Quantitative measurement of business performance and effectiveness allows for optimisation of key business processes which contribute significantly to business performance. Performance data provides the capacity to innovate and grow.

INTEROPERABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	SYSTEM AS SILO

LEVEL	NAME	DESCRIPTION
1	System as silo	Performance monitoring is performed internally with no industry benchmark to make a comparison against. No standardisation.
2	Peer-to-peer	Performance monitoring is measured against other homogenous systems. Peer-to-peer. Guidelines exist which describe interoperability.
3	Distributed	Streamlining of performance monitoring across the entire organisation according to an interoperability framework. Knowledge is shared.
4	Integrated	Integrated performance monitoring. Based on industry benchmarking and external review/assessments between organisations with shared value systems and goals.
5	Universal	Unified performance monitoring. All organisations in the global healthcare interoperability community are continually interoperating.

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Results

D1.1.6 Transparency and accountability

Transparency instils trust confidence in the organisation and their system by the public. Accountability refers to the organisation taking responsibility for its actions. Both transparency and accountability are exercised in a PV context through the clear communication of post authorisation safety studies (PASSs) and patient safety update reports (PSURs) by the MAH. Communication of patient safety information and safety issues should be coordinated with all stakeholders in PV, while maintaining patient confidentiality. National competent authorities should publicise regular reports on the performance of their PV systems as well as the results of regular system audits. Information used in decision-making processes should be made openly available to ensure objective and collaborative decision-making. Transparency addresses how an organisation is observed by outsiders based on the quality of information that the organisation shares with the public.

CAPABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	INITIAL

LEVEL	NAME	DESCRIPTION
1	Initial	Transparency and accountability is not thoroughly understood within the organisation. No comprehensive policy documentation exists addressing transparency and accountability.
2	Managed	Simple policies addressing transparency and accountability exist. Simple risk management plans associated with accountability exist.
3	Defined	Transparency and accountability is understood by individuals in the organisation. The organisation has strong policies in place addressing the transparency of their business practices and understands the value of maintaining a positive sentiment by the external environment.
4	Quantitatively Managed	Individuals take responsibility for their work functions and are held accountable for their actions. The organisation monitors the sentiment of outsiders towards their business practices and adapts the business practices accordingly. The organisation has sound risk management plans to assist with accountability.
5	Optimizing	The organisation considers transparency and accountability as a value. Communication of auditing and assessment outcomes is done in a transparent manner so as to maintain a positive sentiment by the external environment. Strategic level decision making is inclusive of transparency and accountability principles. The organisation has a robust and agile risk management strategy.

INTEROPERABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	SYSTEM AS SILO

LEVEL	NAME	DESCRIPTION
1	System as silo	Localised understanding of transparency and accountability. No standardisation.
2	Peer-to-peer	Common understanding of transparency and accountability exists between some homogenous organisations. Guidelines exist which describe interoperability.
3	Distributed	Streamlining of organisational procedures resulting in a common understanding of transparency and accountability between all homogenous organisations exists.
4	Integrated	Integrated understanding of transparency and accountability across heterogenous organisations with shared value systems and goals.
5	Universal	A universal understanding of transparency and accountability across all interoperating organisations in the interoperability community. All organisations in the global healthcare interoperability community are continually interoperating.

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Results

D1.1.7 Partnerships

Patient safety and PV activities must be considered when forming and managing partnerships. In the case where multiple partner organisations make use of the same PV system, each partner must ensure that the PV system functions to meet their individual regulatory compliance needs. Implementing regulations which detail public-private partnerships specifically for the development of patient safety systems. Regulatory Authorities should clearly communicate the responsibilities and legal requirements of the MAHs within their jurisdiction.

CAPABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	INITIAL

LEVEL	NAME	DESCRIPTION
1	Initial	An initial attempt has been made to identify key partnerships which the organisation should develop.
2	Managed	The organisation has established simple partnerships with all organisations that affect its business operations and value creation. The organisation focusses on building confidence in the partnerships.
3	Defined	The partnerships are managed and trust is established between partner organisations.
4	Quantitatively Managed	Service level agreements are agreed upon across partnerships and allow for quantitative measurement.
5	Optimizing	Strong partnerships with partners sharing in value creation, Partnerships are built on a solid foundation of trust and performance with partners seeking mutual benefit across the partnership.

INTEROPERABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	SYSTEM AS SILO

LEVEL	NAME	DESCRIPTION
1	System as silo	Partnerships are unplanned and unanticipated, no strategy to manage partnerships exists. No standardisation.
2	Peer-to-peer	Guidelines on partnership management are available but specific arrangements are unplanned.
3	Distributed	A common partnership management strategy is developed with the help of an organisational interoperability framework. Streamlining or organisational procedures for knowledge sharing.
4	Integrated	Partnership management strategies of heterogenous organisations encourage the discovery of new partnership opportunities for different organisations.
5	Universal	Goal interoperability between among partnerships. Partnerships support the adaptation of work procedures.

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Results

D1.1.8 Stakeholder communication

Provisions for timely and effective communication of patient safety information or safety concerns to the relevant stakeholders (consumers, HCPs, MAH, RAs, etc.), be it within an organisation or between organisations. This also applies to communication between MAHs and their respective RAs. Coordination and cooperation between the various parties involved in communicating patient safety information, as well as the management of communication tools and channels should seek to improve access to information by those in need of the information. Establish internal and external communication plans to facilitate the communication within your authority and with external stakeholders at national level.

CAPABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	INITIAL

LEVEL	NAME	DESCRIPTION
1	Initial	No formal communication channels exist within the organisation or between the organisation and its external stakeholders.
2	Managed	Simple communication channels exist both internally and externally.
3	Defined	Well defined communication channels exist within the organisation as well as between the organisation and its external stakeholders.
4	Quantitatively Managed	Communication channels are monitored and controlled.
5	Optimizing	Communication channels are well established. Communication channels within the organisation as well as between the organisation and its external stakeholders are continuously improved.

INTEROPERABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	SYSTEM AS SILO

LEVEL	NAME	DESCRIPTION
1	System as silo	No stakeholder communication strategy. Organisation does not interact with any external stakeholders. No standardisation.
2	Peer-to-peer	Peer-to-peer stakeholder communication based on simple agreements between homogenous organisations. Guidelines exist which describe interoperability.
3	Distributed	Stakeholder communication is developed with the help of an organisational interoperability framework. Streamlining or organisational procedures for knowledge sharing.
4	Integrated	Stakeholder communication activities are linked between heterogenous organisations and interoperability standards are implemented, allowing for the sharing of benefits and value between organisations serving a common goal.
5	Universal	A universal approach to stakeholder communication. All organisations in the global healthcare interoperability community are continually interoperating. Supporting adaptation and continuous improvement of work procedures.

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Results

D1.1.9 Organisational strategy alignment

It is important that the organisation has a shared understanding of the PV operating model across all levels of the organisation as well as a common understanding of the role of the organisation within the global patient safety system. Different functional units of an organisation, such as manufacturing, sales and marketing, and quality control, may have contradicting goals and incentive structures, which do not focus on patient safety. Implementing best practices and the alignment of operational activities. Organisations must develop clearly defined roles and responsibilities.

CAPABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	INITIAL

LEVEL	NAME	DESCRIPTION
1	Initial	Business objectives are not well understood by the various departments within the organisation.
2	Managed	Business objectives are understood within departments. Gaps exist between business objectives and business processes.
3	Defined	Business objectives are explicitly linked to business processes
4	Quantitatively Managed	Business processes are adapted to support business objectives and a shared understanding of the linkage between business objectives and business processes is understood within and across organisational departments.
5	Optimizing	Strategy development is inclusive of all relevant departments, each of which contributing to support strategy development.

INTEROPERABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	SYSTEM AS SILO

LEVEL	NAME	DESCRIPTION
1	System as silo	Business objectives are developed within the confines of the localised system setting. No standardisation.
2	Peer-to-peer	Work processes and business objectives are linked based on simple agreements in a peer-to-peer manner.
3	Distributed	Organisational strategy alignment is guided by an organisational interoperability framework. Streamlining or organisational procedures for knowledge sharing.
4	Integrated	Organisational strategies are linked between heterogenous organisations and interoperability standards are implemented, allowing for the sharing of benefits and value between organisations serving a common goal.
5	Universal	Goal interoperability between all organisations in the global healthcare interoperability community. Universal alignment of organisational strategies regarding patent safety. All organisations in the global healthcare interoperability community are continually interoperating.

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Results

D1.1.10 Building a culture of Safety

A system of shared actions, values, and beliefs that develop within an organisation and are transferred to new members as the way to perceive, think, and feel in the organisation. Attitudes and behaviors of organisational workforce towards patient safety. Moving from a culture of compliance to a culture of commitment. The key to developing a strong organisational PV culture is to support and manage the natural social and behavioral aspects of the individuals interactions, rather than attempt to force cultural change by decree. A strong culture of safety can help shape the way in which the organisation views PV, from that of a collection of compliance and risk mitigation activities, to a means of developing a set of standard business procedures which yield a competitive advantage.

CAPABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	INITIAL

LEVEL	NAME	DESCRIPTION
1	Initial	Patient safety culture is inconsistently managed. Patient safety is not considered a goal of the organisation.
2	Managed	Simple commitment from management to improving patient safety culture within the organisation. Patient safety culture is a culture of compliance.
3	Defined	Management considers individual societal culture, organisational culture and the interaction between the two. Patient safety culture evolves from a culture of compliance to a culture of commitment.
4	Quantitatively Managed	Leadership uses patient safety outcomes to promote patient safety culture and acts on patient safety improvement initiatives. Visible commitment to patient safety throughout organisation.
5	Optimizing	Patient safety culture is firmly rooted in the organisation across all levels and decision making across the health system is patient safety centred. Patient safety is considered an organisational value. Patient safety culture follows a culture of commitment and development.

INTEROPERABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	SYSTEM AS SILO

LEVEL	NAME	DESCRIPTION
1	System as silo	No formal approach to building a culture of patient safety. No standardisation.
2	Peer-to-peer	Safety culture extends beyond the local setting and is aligned with and linked across homogenous organisations. Guidelines exist which describe interoperability.
3	Distributed	A culture of patient safety is developed with the help of an organisational interoperability framework. Streamlining or organisational procedures for knowledge sharing.
4	Integrated	Patient safety culture extends and is shared between heterogenous organisations and interoperability standards are implemented, allowing for the sharing of benefits and value between organisations serving a common goal.
5	Universal	Patient safety culture is a universal goal of all organisations in the global healthcare interoperability community. All organisations in the global healthcare interoperability community are continually interoperating. Supporting adaptation and continuous improvement of work procedures.

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Results

D1.1.11 Organisational change management

Operational processes are clearly linked to performance outcomes and goals. Organisations should seek to embed a culture of continuous improvement. Change management processes need to be established to guide the adoption of newly identified best practices and updated work procedures.
Change management is critical when dealing with an ever-changing business environment and the constant introduction of new technologies.

CAPABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	INITIAL

LEVEL	NAME	DESCRIPTION
1	Initial	Initial attempt at change management is implemented inconsistently. Recognised need for change management.
2	Managed	Simple, but effective change management is applied in isolated projects.
3	Defined	Comprehensive change management is applied simultaneously over multiple projects within the organisation.
4	Quantitatively Managed	Organisation makes use of standards and methods for broadly managing and leading change.
5	Optimizing	Change management is evident across all levels of the organisation and contributes actively to the success of the organisation in meeting its business objectives.

INTEROPERABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	SYSTEM AS SILO

LEVEL	NAME	DESCRIPTION
1	System as silo	Organisational change is not considered a priority as the system is isolated and therefore not influenced by changes in the external environment. No standardisation.
2	Peer-to-peer	Guidelines on how organisational change management must occur with respect to interoperability. Guidelines exist which describe interoperability.
3	Distributed	Organisational change is managed with the help of an organisational interoperability framework. Streamlining or organisational procedures for knowledge sharing.
4	Integrated	Organisational change management activities are linked between heterogenous organisations and interoperability standards are implemented, allowing for the sharing of benefits and value between organisations serving a common goal.
5	Universal	Goal interoperability between all organisations in the global healthcare interoperability community. All organisations in the global healthcare interoperability community are continually interoperating. Supporting adaptation and continuous improvement of work procedures.

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Results

D1.2.1 Financial management

Dedicated budget available for PV relate activities. The legal and administrative systems and procedures put in place permitting a government ministry and its agencies and organizations to conduct activities that ensure the correct use of public funds, and which meet defined standards of probity and regularity. Activities include management and control of public expenditures, financial accounting, reporting, and asset management. Proactive investment in technologies which can be leveraged to improve patient safety.

CAPABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	INITIAL

LEVEL	NAME	DESCRIPTION
1	Initial	Initial attempt at financial management for patient safety related activities. Recognised need for appropriate financial management.
2	Managed	Simple, but complete financial management strategy. Finances are managed in an unpredictable and reactive manner.
3	Defined	Proactive financial management for patient safety related activities. Dedicated budget developed by organisation government to support the achievement of project and organisational performance objectives.
4	Quantitatively Managed	Finances are quantitatively managed. Expenditures are monitored against budget and finances are subjected to regular audits. Proactive investment in innovation and technology.
5	Optimizing	Financial management system is owned, reviewed and actively updated by a wide range of stakeholders.

INTEROPERABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	SYSTEM AS SILO

LEVEL	NAME	DESCRIPTION
1	System as silo	Financial management strategy is isolated and localised within the confines of the system setting. No standardisation.
2	Peer-to-peer	Financial management activities are linked between homogenous organisations through simple agreements. Guidelines exist which describe interoperability.
3	Distributed	Financial management is guided by an organisational interoperability framework. Streamlining or organisational procedures for knowledge sharing.
4	Integrated	Financial management activities are linked between heterogenous organisations and interoperability standards are implemented, allowing for the sharing of benefits and value between organisations serving a common goal.
5	Universal	Goal interoperability between all organisations in the global healthcare interoperability community. All organisations in the global healthcare interoperability community are continually interoperating. Supporting adaptation and continuous improvement of work procedures.

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Results

D1.2.2 Financial resource mobilisation

All activities involved in securing new and additional financial resources for an organization (in this case, the HIS). It also involves making better use of and maximising existing financial resources. The existence of any regular financial provisions. Provision of funding demonstrates government commitment to patient safety and can directly improve conditions in the workplace environment which ultimately improves HCPs attitudes towards patient safety.

CAPABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	INITIAL

LEVEL	NAME	DESCRIPTION
1	Initial	Funding for patient safety activities is acquired in an unstructured, inconsistent manner.
2	Managed	Simple, but complete financial resource mobilisation plan.
3	Defined	Financial resource mobilisation is tailored to address project and work characteristics. Supports project and organisational performance objectives.
4	Quantitatively Managed	Financial resource mobilisation has matured to ensure continuous and secure funding for all business processes involved in patient safety.
5	Optimizing	Financial resource mobilisation strategy is owned, reviewed and actively updated by a wide range of stakeholders.

INTEROPERABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	SYSTEM AS SILO

LEVEL	NAME	DESCRIPTION
1	System as silo	Financial resource mobilisation strategy is isolated and localised within the confines of the system setting. No standardisation.
2	Peer-to-peer	Financial resource mobilisation activities are linked between homogenous organisations through simple agreements. Guidelines exist which describe interoperability.
3	Distributed	Financial resource mobilisation strategy is guided by an organisational interoperability framework. Streamlining or organisational procedures for knowledge sharing.
4	Integrated	Financial resource mobilisation activities are linked between heterogenous organisations and interoperability standards are implemented, allowing for the sharing of benefits and value between organisations serving a common goal.
5	Universal	Goal interoperability between all organisations in the global healthcare interoperability community. Universal financial resource mobilisation strategy regarding patent safety. All organisations in the global healthcare interoperability community are continually interoperating. Supporting adaptation and continuous improvement of work procedures.

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Results

D1.3.1 Regulatory Compliance

All organisations must comply with patient safety reporting requirements which are imposed by the relevant Regulatory Authority. Compliance monitoring policies and strategies. This includes reviews, inspections, and audits which can be conducted regularly internally or by an external actor.
A good compliance strategy reduces the risk of business disruption, litigation costs, and reputational damage.

CAPABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	INITIAL

LEVEL	NAME	DESCRIPTION
1	Initial	The organisation is unaware of the full extent of its compliance obligations. Compliance is assessed ad-hoc or by means of external audits and assessments.
2	Managed	The organisations understands the full extent of its compliance obligations. A catalogue of compliance requirements is created. Compliance is managed in an unpredictable and reactive manner.
3	Defined	Internal compliance capability development. SOPs and a record management system is in place to manage compliance. Compliance is proactively managed and sustainable.
4	Quantitatively Managed	Internal compliance capabilities are aligned with external auditing and assessment guidelines. The organisation has the capability to predict potentially impactful regulatory changes.
5	Optimizing	Compliance and the associated risks are well understood throughout the organisation and outcomes from compliance processes are used to inform strategic level decision making.

INTEROPERABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	SYSTEM AS SILO

LEVEL	NAME	DESCRIPTION
1	System as silo	Regulatory compliance is measured in isolation and is localised to the system setting. No standardisation.
2	Peer-to-peer	Regulatory compliance work processes are linked between homogenous organisations through simple agreements. Guidelines exist which describe interoperability.
3	Distributed	Regulatory compliance is assessed across homogenous interoperating organisations with the help of an interoperability framework. Streamlining of organisational procedures.
4	Integrated	Regulatory compliance activities are linked between heterogenous organisations and interoperability standards are implemented, allowing for the sharing of benefits and value between organisations serving a common goal.
5	Universal	Goal interoperability between all organisations in the global healthcare interoperability community. Universal regulatory compliance regarding patent safety. All organisations in the global healthcare interoperability community are continually interoperating. Supporting adaptation and continuous improvement of work procedures.

MJ Schurer, L Louw, L Bam, IH de Kock

Results

D1.3.2 Resource efficiency and business sustainability

Efficient resource utilisation improves system outputs by maximising the supply of inputs and minimising wasted resource expenses. Resource efficiency means achieving the desired outcomes in a sustainable manner. Business sustainability deals with the ability of an organisation to meet the demands of the present without effecting its ability to meet the demands of the future. Business sustainability typically involves financial, social, and environmental components.

CAPABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	INITIAL

LEVEL	NAME	DESCRIPTION
1	Initial	Ad hoc sustainability policies and practices in place. Resource efficiency not considered a priority.
2	Managed	Simple resource efficiency and business sustainability policies and practices are in place. Implemented on a per project basis.
3	Defined	Proactive efforts across the organisation to improve resource efficiency and business sustainability in all business operations.
4	Quantitatively Managed	Organisation and business principles are aligned with resource efficiency and business sustainability. Increased profitability is directly associated with resource efficiency and business sustainability.
5	Optimizing	Strategic level decision making includes resource efficiency and business sustainability.

INTEROPERABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	SYSTEM AS SILO

LEVEL	NAME	DESCRIPTION
1	System as silo	Resource efficiency and business sustainability activities are isolated and localised to the system setting. No standardisation.
2	Peer-to-peer	Resource efficiency and business sustainability activities are linked across homogenous organisations through simple agreements. Guidelines exist which describe interoperability.
3	Distributed	Shared knowledge regarding resource efficiency and business sustainability across homogenous organisations which serve a common goal, through streamlining of organisational procedures.
4	Integrated	Resource efficiency and business sustainability activities are linked between heterogenous organisations and interoperability standards are implemented, allowing for the sharing of benefits and value between organisations serving a common goal.
5	Universal	Goal interoperability between all organisations in the global healthcare interoperability community. Universal alignment of resource efficiency and business sustainability strategies regarding patent safety. All organisations in the global healthcare interoperability community are continually interoperating.

MJ Schurer, L Louw, L Bam, IH de Kock

Results

D1.3.3 Data management

Data management consists of the development, execution, and supervision of plans, policies, programs, and practices that control, protect, deliver, and enhance the value of data and information assets for decision making.

Data management includes procedures on how data are captured, stored, analysed, transmitted, and packaged for use across the data supply chain.

CAPABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	INITIAL

LEVEL	NAME	DESCRIPTION
1	Initial	Data management is performed ad hoc and inconsistently. A recognised need for formal data management policies and actions.
2	Managed	Simple, but complete set of policies and practices addressing the management of data.
3	Defined	Standard operating procedures are in place for the management of data. A detailed plan of action is developed to migrate from a paper based system to an electronic data management system. The necessary privacy and security measures are included.
4	Quantitatively Managed	Data management processes are disseminated throughout the organisation so as to inform all stakeholders on how their work processes are affected. Data storage and data exchanges are formalised and monitored.
5	Optimizing	The data management system allows for continuous monitoring of access and use. Electronic data exchange is considered the default method of transferring data both internally and externally. The data management system is continuously improved upon.

INTEROPERABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	SYSTEM AS SILO

LEVEL	NAME	DESCRIPTION
1	System as silo	Data management is confined to the local system setting. No standardisation.
2	Peer-to-peer	Simple agreements regarding data management are implemented allowing simple electronic exchange of data between homogenous systems. Guidelines exist which describe interoperability.
3	Distributed	Data management is guided by an organisational interoperability framework. Streamlining or organisational procedures for knowledge sharing.
4	Integrated	Data management activities are linked between heterogenous organisations and interoperability standards are implemented, allowing for the sharing of benefits and value between organisations serving a common goal.
5	Universal	Goal interoperability between all organisations in the global healthcare interoperability community. Universal alignment of data management strategies regarding patent safety. All organisations in the global healthcare interoperability community are continually interoperating.

MJ Schurer, L Louw, L Bam, IH de Kock

Results

D1.4.1 Human resources policy

The existence of policy documents that specify the roles and responsibilities of the relevant PV staff. Including the designation of a Qualified Person for Pharmacovigilance (QPPV). A set of principles, guidelines, and norms that an organisation adopts to help manage its employees.

CAPABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	INITIAL

LEVEL	NAME	DESCRIPTION
1	Initial	Roles and responsibilities undefined with work processes being completed inconsistently, on an ad-hoc basis.
2	Managed	Simple, but complete set of defined roles and responsibilities with dedicated staff.
3	Defined	Well defined roles and responsibilities with dedicated staff of adequate competency.
4	Quantitatively Managed	Well defined roles and responsibilities with dedicated, fully competent staff, whose performance is measurable with performance indicators/metrics.
5	Optimizing	Performance of human resources is optimal and consistent. Outcomes of quality and process performance objectives are used when reviewing and developing new roles and responsibilities.

INTEROPERABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	SYSTEM AS SILO

LEVEL	NAME	DESCRIPTION
1	System as silo	No formal interoperability framework addressing human resources policy. HR policy is developed within the confines of the localised system setting. No standardisation.
2	Peer-to-peer	Guidelines on interoperability exist but specific arrangements relating to human resources policy are unplanned.
3	Distributed	Human resources policy is developed according to an organisational interoperability framework, based on organisations with shared goals and common roles and responsibilities.
4	Integrated	Integrated approach to human resources policy development across all heterogenous organisations with shared value systems and goals in the interoperability community.
5	Universal	A universal approach to human resources policy development. All organisations in the global healthcare interoperability community are continually interoperating. Supporting adaptation and continuous improvement of work procedures.

MJ Schurer, L Louw, L Bam, IH de Kock

Results

D1.4.2 Human resources capacity

Availability of adequate personnel with relevant characteristics, attributes, and capabilities to perform the tasks or sets of tasks outlined by the organisations PV operations and policy documents. This includes people across all stages of the system life cycle, from aspects such as design, development, implementation, and use of the system. (e.g. system architect designers, software developers, implementation and training personnel, as well as HCPs.)

CAPABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	INITIAL

LEVEL	NAME	DESCRIPTION
1	Initial	Patient safety work processes are performed ad hoc, in an inconsistent manner by unqualified individuals.
2	Managed	Patient safety work processes are identified and assigned to individuals in a structured manner.
3	Defined	Standardised roles and responsibilities are entrusted to qualified and capable personnel.
4	Quantitatively Managed	Designated staff across all levels of the organisation with the appropriate responsibilities, accountability, and authority for conducting patient safety activities. Patient safety staff are motivated to perform and have a high level of engagement.
5	Optimizing	Patient safety staff take full control over the development of their career and the improvement of their work. Patient safety staff are self-motivating and assist HR with attracting world-class talent.

INTEROPERABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	SYSTEM AS SILO

LEVEL	NAME	DESCRIPTION
1	System as silo	HR capacity is managed within the confines of the localised system setting. No standardisation.
2	Peer-to-peer	HR capacity processes of homogenous systems linked and guided by interoperability guidelines.
3	Distributed	HR capacity is developed with the help of an organisational interoperability framework. Streamlining or organisational procedures for knowledge sharing.
4	Integrated	HR capacity is sufficient that all heterogenous organisations with shared value systems and goals in the interoperability community are able to share benefits and value.
5	Universal	Continuous improvement in HR capacity ensure continuous interoperation between all organisation in the global healthcare interoperability community. Supporting adaptation and continuous improvement of work procedures.

MJ Schurer, L Louw, L Bam, IH de Kock

Results

D1.4.3 Human resources capacity development

Awareness, education, and training initiatives aimed at the development of a strong PV culture within the organisation. An organised activity with clear learning outcomes that aims to impart knowledge and skills, shape attitudes, and develop specific competencies and capabilities in personnel. Provision of guidance on the importance of safe practices and procedures for patient safety. Increased sensitisation of healthcare workers on the causes and prevention of adverse events should form part of the continuous professional development of all HCPs. Patient safety training should form part of the curricula of healthcare training institutions.

CAPABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	INITIAL

LEVEL	NAME	DESCRIPTION
1	Initial	Emerging need for professional development of patient safety workforce. Ad hoc and incidental training occurs by means of mentoring and apprenticeships.
2	Managed	Simple HR capacity development plan in place which targets core competencies.
3	Defined	Formal, future-focussed, talent development programs implemented.
4	Quantitatively Managed	A culture of learning and professional development becomes embedded in the organisation. Performance support is available to assist with learning.
5	Optimizing	Continuous professional development. HR capacity development strategy is aligned with business strategy, resulting in an agile and future focussed workforce.

INTEROPERABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	SYSTEM AS SILO

LEVEL	NAME	DESCRIPTION
1	System as silo	No formal HR capacity development framework in place. HR capacity is developed on an ad hoc basis, unpredictably.
2	Peer-to-peer	HR capacity development processes of homogenous organisations linked and guided by interoperability guidelines.
3	Distributed	HR capacity development strategy is developed with the help of an organisational interoperability framework. Streamlining or organisational procedures for knowledge sharing.
4	Integrated	HR capacity development is linked across various heterogenous organisations serving a common goal for the sharing of benefits and value.
5	Universal	HR capacity development is universal and ensures continuous interoperation between all organisation in the global healthcare interoperability community. Supporting adaptation and continuous improvement of work procedures.

MJ Schurer, L Louw, L Bam, IH de Kock

Results

D2.1.1 Data Capture

Methods of capturing data associated with the suspected adverse drug reaction and the technologies involved. The WHO states that an ADR reporting form is one of the minimum requirements for a functioning spontaneous reporting system. Structured forms, electronic vs paper based, etc.

CAPABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	INITIAL

LEVEL	NAME	DESCRIPTION
1	Initial	Paper-based system for capturing patient safety information.
2	Managed	Simple electronic form to capture patient safety information.
3	Defined	Web-based data capture via a "smart"/interactive form with standard data elements.
4	Quantitatively Managed	Electronic data capture via computer, web portal or mobile application.
5	Optimizing	Automated data capture from other information systems (EHRs, pharmacy, labs etc.)

INTEROPERABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	SYSTEM AS SILO

LEVEL	NAME	DESCRIPTION
1	System as silo	Single technology used for data capture. Data capture occurs in an unstructured way and requires manual data integration. No standardisation.
2	Peer-to-peer	Data capture is performed electronically and adheres to standards agreed upon by homogenous systems. Guidelines exist which describe interoperability.
3	Distributed	Distributed data capture standard. Guided by an interoperability framework. Streamlining of data capture over a central server linking shared logical data models.
4	Integrated	Data capture according to international standards to allow interoperability between various heterogenous systems which serve a common goal.
5	Universal	Data capture standards and applications are fully shared and distributed. All organisations in the global healthcare interoperability community are continually interoperating. Supporting adaptation and continuous improvement of work procedures.

MJ Schurer, L Louw, L Bam, IH de Kock

Results

D2.1.2 Data Storage and Aggregation

Databases and database management. How data is aggregated for statistical analysis, as well as how duplication errors are avoided. The WHO states that an ADR report database is one of the minimum requirements for a functioning spontaneous reporting system.
The methods of aggregating data for statistical analysis, as well as methods for duplicate detection are important when considering the spontaneous reporting system.

CAPABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	INITIAL

LEVEL	NAME	DESCRIPTION
1	Initial	No electronic database, paper based ADR reports.
2	Managed	Simple electronic storage of ADR reports, Microsoft Excel spreadsheet.
3	Defined	Dedicated electronic ICSR database is established.
4	Quantitatively Managed	ICSR database compatible with medical terminology directories (e.g. MedDRA), access and usage monitoring, validity and duplication detection capability.
5	Optimizing	ICSR database with backwards and forewords compatibility for the ICH ICSR E2B (R2/R3) standard reporting format.

INTEROPERABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	SYSTEM AS SILO

LEVEL	NAME	DESCRIPTION
1	System as silo	Database is designed and developed within the confines of the localised system setting. Data is stored manually. No standardisation.
2	Peer-to-peer	Database receives and stores data from more than one IT system via simple agreements for simple electronic data exchange, Guidelines exist which describe interoperability.
3	Distributed	Functional linking of databases which share logical data models across organisations. Standardised safety, security and privacy protocols.
4	Integrated	Database receives and stores data from multiple heterogenous IT systems. Standardised safety, security and privacy protocols.
5	Universal	Database is fully integrated with international guidelines, standards and best practices. Continuously reviewed and improved, ultimately contributing to the evolution of the global healthcare interoperability community. Supporting adaptation and continuous improvement of work procedures.

MJ Schurer, L Louw, L Bam, IH de Kock

Results

D2.1.3 Workflows

Workflows describe the necessary sequential steps which need to be taken when performing the business processes. Workflows typically involve the use of Standard Operating Procedures (SOPs). In the context of a spontaneous reporting system this includes receiving the information, case entry, duplicate checking, case registration, case triage, data entry and narrative write up, review, case closure and the transmission of the ICSR.

CAPABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	INITIAL

LEVEL	NAME	DESCRIPTION
1	Initial	Initial attempt at defining workflows has been made but are not comprehensive in nature.
2	Managed	Simple, but complete set of patient safety related workflows has been defined.
3	Defined	Workflows are well defined and standard operating procedures have been developed.
4	Quantitatively Managed	Quantitative methods are employed to understand performance variation by focussing on process performance objectives.
5	Optimizing	The use of quantitative techniques allow for optimisation and continuous improvement of workflow management and developing and implementing SOPs.

INTEROPERABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	SYSTEM AS SILO

LEVEL	NAME	DESCRIPTION
1	System as silo	Workflows are developed within the confines of the localised system setting. No standardisation.
2	Peer-to-peer	Workflows are partially interoperable with other homogenous systems based on simple agreements for simple data exchange. Guidelines exist which describe interoperability.
3	Distributed	Workflows are linked across facilities of an organisations in the same country and are aligned to achieve a common objective.
4	Integrated	Workflows from heterogenous organisations which serve a common goal are linked together for shared benefits and value interoperability.
5	Universal	Universally agreed upon workflows which support the adaptation and continuous improvement of work procedures. All organisations in the global healthcare interoperability community are continually interoperating.

MJ Schurer, L Louw, L Bam, IH de Kock

Results

D2.1.4 Data Presentation/Transmission

The format in which data is presented to the subsequent entity in the chain of PV communication. Currently the best practice is the ICH E2B(R3) standard for the electronic transmission of ICSRs with backwards/forwards compatibility.

CAPABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	INITIAL

LEVEL	NAME	DESCRIPTION
1	Initial	Paper-based ADR reports mailed via a postal service.
2	Managed	ICSR sent as attachment via e-mail, but not E2B compliant.
3	Defined	E2B compliant ICSR sent via e-mail.
4	Quantitatively Managed	ICSR sent to the UMC via the web-based VigiFlow reporting tool.
5	Optimizing	E2B compliant ICSR transmitted via a proprietary gateway application, adhering to the ICH ICSR E2B (R3) business rules for the electronic transmission of ICSRs.

INTEROPERABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	SYSTEM AS SILO

LEVEL	NAME	DESCRIPTION
1	System as silo	Data transmission is performed manually due to isolated use of technology. No standardisation.
2	Peer-to-peer	Simple electronic data exchange between homogenous systems with discretional pre- and post-exchange data handling. Guidelines exist which describe interoperability.
3	Distributed	Distributed data transmission standard. Streamlining of transmission over a central server linking shared logical data models.
4	Integrated	Data transmission is according to industry standards, allowing the exchange of data between independent heterogenous systems.
5	Universal	Data transmission is according to universally agreed upon standards, and can be between any systems in the global healthcare interoperability community. Supporting adaptation and continuous improvement of work procedures.

MJ Schurer, L Louw, L Bam, IH de Kock

Results

D2.2.1 Data Standards

Data standards is inclusive of knowledge representation and terminology standards. Provisions for the inclusion of all relevant structured data useful to assess an individual case. Knowledge representation refers to how medical knowledge is represented within an information system/application context. Collaboration among system users and developers is critical when managing inconsistent knowledge bases. Terminology standards provide specific codes for terminologies and classifications for clinical concepts such as diseases and medications. The terminology systems assign a unique code to a specific disease or entity. An appropriate MedDRA term should be provided in the lowest level term for the drug characterisation along with the resulting suspected adverse reaction. Compliance with standardised medical data content standards such as WHO-ART and MedDRA.

CAPABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	INITIAL

LEVEL	NAME	DESCRIPTION
1	Initial	No formal standards are adhered to, any standards that are adhered to are incidental and on an ad hoc basis.
2	Managed	The need for data standards is recognised by the organisation and simple data standards governing the encoding of electronic data are adhered to.
3	Defined	A comprehensive portfolio of data standards is adopted by the organisation. These data standards specifically address all the relevant topics relating to the exchange of electronic healthcare data. Knowledge representation and terminology standards are adhered to.
4	Quantitatively Managed	The portfolio of data standards has been disseminated throughout the organisation. Compliance is measured by an external auditing body and certification is awarded accordingly.
5	Optimizing	Data standards are regularly reviewed and updated to be consistent with best practices and to ensure interoperability with other health information systems.

INTEROPERABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	SYSTEM AS SILO

LEVEL	NAME	DESCRIPTION
1	System as silo	Data standards are specific to a proprietary system. No interaction between systems negates the need for data standards. No standardisation.
2	Peer-to-peer	Simple data standards are implemented allowing the electronic exchange of data between homogenous systems.
3	Distributed	Distributed portfolio of data standards throughout the organisation. Linking of systems for a common objective. Standardised data protection, security, and privacy protocols in place.
4	Integrated	International standards and best practices adhered to by the organisation, allowing for the integration of heterogenous systems which serve a common goal.
5	Universal	Universally agreed upon and implemented standards which support the adaptation and continuous improvement of work procedures. All organisations in the global healthcare interoperability community are continually interoperating.

MJ Schurer, L Louw, L Bam, IH de Kock

Results

D2.2.2 Information content

The data encoded in an ICSR must collectively represent information that is interpreted in the same way by the ICSR sender and receiver. The information that is encoded in the ICSR for an ADR report. Standard data elements, provisions for free text narratives.
Minimal Information Model for Patient Safety Incident Reporting and Learning Systems. The ICH ICSR E2B (R3) standard, current best practice.

CAPABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	INITIAL

LEVEL	NAME	DESCRIPTION
1	Initial	No set of minimum information/data elements adhered to. A recognised need for a minimum set of information/data elements.
2	Managed	The ICSR form has a simple but complete set of basic data elements which constitute the minimum acceptable information.
3	Defined	Electronic ICSR form with a standard set of data elements. E.g. the Minimal Information Model for Patient Safety (MIM PS). No provision for free text narrative.
4	Quantitatively Managed	Electronic ICSR form compliant with the ICH E2B (R3) standard, with a comprehensive set of data elements and the provision for a free text narrative.
5	Optimizing	A system wherein the sought after information is pulled through on an as requested basis. Through correct harmonisation of systems and standards, information can be requested as opposed to reported or "pushed" to the entity requesting the information. Thus allowing for the inclusion of any and all information available.

INTEROPERABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	SYSTEM AS SILO

LEVEL	NAME	DESCRIPTION
1	System as silo	System as silo means no interaction with other systems and therefore no standard in place for the information content of the ICSR. No standardisation.
2	Peer-to-peer	Simple agreements between two homogenous systems regarding information content of the ICSR.
3	Distributed	Standard information content model developed for the transmission of ICSRs between homogenous systems.
4	Integrated	Shared information model across various heterogenous systems to allow for transmission of ICSRs within the interoperable community.
5	Universal	A common information model is universally distributed allowing the transmission of ICSRs between any organisations in the interoperable community. All organisations in the global healthcare interoperability community are continually interoperating. Supporting adaptation and continuous improvement of work procedures.

MJ Schurer, L Louw, L Bam, IH de Kock

Results

D2.2.3 Data protection, privacy, and security standards

Data protection, privacy and security standards associated with the exchange of patient safety information. Measures to disable unauthorised access of information, manipulation, modification or deletion of information. E.g. The EU General Data Protection Regulation (GDPR).

CAPABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	INITIAL

LEVEL	NAME	DESCRIPTION
1	Initial	Identified need for data protection, privacy and security standards. No standards are implemented or adhered to consistently.
2	Managed	Some data protection, privacy and security standards are incidentally and unpredictably adhered to.
3	Defined	Specific data protection, privacy and security standards are identified and adhered to.
4	Quantitatively Managed	Auditing and compliance monitoring of the data protection, privacy and security standards allows for quantitative feedback.
5	Optimizing	Management monitors compliance with data protection, privacy and security standards. Any issues of non-compliance are identified and remedial action is taken to ensure compliance in a timely manner

INTEROPERABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	SYSTEM AS SILO

LEVEL	NAME	DESCRIPTION
1	System as silo	System as silo, therefore no data protection, privacy, and security standards are in place. No standardisation.
2	Peer-to-peer	Data protection, privacy, and security standards are based on simple agreements for the simple exchange of electronic data between homogenous organisations.
3	Distributed	Data protection, privacy, and security standards are selected and implemented based on an interoperability framework.
4	Integrated	Common data protection, privacy, and security standards are adhered to by various heterogenous organisations which serve a common goal.
5	Universal	Universally agreed upon and implemented data protection, privacy, and security standards which support the adaptation and continuous improvement of work procedures.

MJ Schurer, L Louw, L Bam, IH de Kock

Results

D2.2.4 Information exchange and interoperability standards

Standards which govern the transmission, organisation and interpretation of electronic data. This includes messaging standards, document standards, application standards, conceptual standards, and architecture standards.
These standards are developed by SDOs such as International Standards Organisation (ISO), European Committee for Standardisation (CEN), Health Level Seven (HL7), and OpenEHR.
For interoperability to occur, the interacting ICT systems must agree on the use of standard messaging formats.

CAPABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	INITIAL

LEVEL	NAME	DESCRIPTION
1	Initial	No formal standards are adhered to, any standards that are adhered to are incidental and on an ad hoc basis.
2	Managed	The need for interoperability is recognised and simple initiatives are employed to manage interoperability.
3	Defined	Interoperability is understood as a business goal and competitive advantage. Formal interoperability standards are selected and adhered to. Organisational structures are in place to guide interoperability.
4	Quantitatively Managed	The organisation conducts interoperability compliance assessments to gain insight into which aspects of interoperability require attention. The organisation implements and adheres to a framework for interoperability compliance.
5	Optimizing	The advantages of interoperability are widely understood throughout the organisation and are linked to specific business practices. The organisation leverages these advantages to improve overall efficiency and the bottom line. Information exchange and interoperability standards are regularly reviewed and updated to be consistent with best practices.

INTEROPERABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	SYSTEM AS SILO

LEVEL	NAME	DESCRIPTION
1	System as silo	Information exchange and interoperability standards not implemented or adhered to because the system works without interaction with other systems. No standardisation.
2	Peer-to-peer	Information exchange and interoperability standards are implemented allowing the electronic exchange of data between homogenous systems.
3	Distributed	Information exchange and interoperability standards are selected and implemented according to an interoperability framework for organisations with shared goals, and aligned roles and responsibilities.
4	Integrated	Common information exchange and interoperability standards are implemented across various heterogenous systems, allowing for the sharing of benefits and value between organisations serving a common goal.
5	Universal	Universally adopted information exchange and interoperability standards across all organisations participating in the global healthcare interoperability community. All organisations in the global healthcare interoperability community are continually interoperating.

MJ Schurer, L Louw, L Bam, IH de Kock

Results

D3.1.1 ICT Hardware

The physical hardware needed to support the operation of a spontaneous reporting system. This hardware includes computers, monitors, data input devices/peripherals (mouse, keyboard, etc.), as well as the appropriate cabling and availability of power.

CAPABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	INITIAL

LEVEL	NAME	DESCRIPTION
1	Initial	The organisation has inadequate hardware to support patient safety, but is aware of the need for appropriate ICT infrastructure.
2	Managed	Simple, but complete assessment of ICT infrastructure needs for supporting patient safety, and a simple but complete infrastructure.
3	Defined	The organisation has identified the specific hardware components that directly support the business processes related to patient safety.
4	Quantitatively Managed	The organisation conducts regular reviews of hardware capabilities and performance to ensure that performance objectives are met.
5	Optimizing	The organisations ICT hardware infrastructure meets international standards. Policies are in place to ensure optimal functioning and maintenance of ICT hardware, allowing for continuous improvement.

INTEROPERABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	SYSTEM AS SILO

LEVEL	NAME	DESCRIPTION
1	System as silo	Hardware across different operating locations of the organisation is not standardised and does not allow for the exchange of patient safety information. No standardisation.
2	Peer-to-peer	Hardware at different operating locations of the organisation allows for simple data exchange and the linking of business processes.
3	Distributed	Hardware at different operating locations of the organisation allows for linking of business processes which support the common goal of improved patient safety. Safety, security, and privacy standards are implemented.
4	Integrated	Hardware across different operating locations of different organisations allows for linking of systems. Integration of heterogenous systems which serve a common goal.
5	Universal	Hardware allows for complete integration with international guidelines, standards and best practices. Continuously reviewed and improved, ultimately contributing to the evolution of the international landscape. Supporting adaptation and continuous improvement of work procedures.

MJ Schurer, L Louw, L Bam, IH de Kock

Results

D3.1.2 Network

The existence of the appropriate IT infrastructure to enable the efficient and effective transmission of ICSRs whether it be over local area network (LAN) within a facility or wide area network (WAN) across facilities or organisation in different geographical locations.

CAPABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	INITIAL

LEVEL	NAME	DESCRIPTION
1	Initial	The organisation has an inadequate network to support the optimal functioning of an information system.
2	Managed	Simple, but effective IT communications network is operational.
3	Defined	The organisation has assessed its networking requirements. An implementation plan is in place to improve the efficiency of the IT communications network.
4	Quantitatively Managed	The performance of the organisations IT communication network is measured against performance objectives.
5	Optimizing	The organisations IT communications networking capabilities are in line with international standards. Functioning optimally and reliably, and subjected to regular testing and performance reviews.

INTEROPERABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	SYSTEM AS SILO

LEVEL	NAME	DESCRIPTION
1	System as silo	System as silo means that no networking ability is in place and no interaction with other systems in performed. No standardisation.
2	Peer-to-peer	Simple agreements regarding LAN capabilities for simple peer-to-peer exchange of electronic data within an organisation.
3	Distributed	Distributed WAN capability to allow network communication between homogenous systems. Streamlining of organisational procedures. Communication over a central server,
4	Integrated	Integrated WAN capabilities enable the integration of heterogenous systems which serve a common goal. Safety, security, and privacy standards are monitored closely.
5	Universal	Universal communications network established for the exchange of electronic healthcare data. Systems and applications can connect freely and exchange data where permissible, without necessarily serving a common goal. Supporting adaptation and continuous improvement of work procedures.

MJ Schurer, L Louw, L Bam, IH de Kock

Results

D3.1.3 Development and Maintenance

Results

Proactive efforts to ensure that the technologies and standards used are maintained and evolved to continually meet the ever-changing needs of the system. This dimension refers to the development and maintenance of technologies and standards to ensure optimal performance of the spontaneous reporting system. It is important to note that maintenance involves different activities at the local and global levels.

CAPABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	INITIAL

LEVEL	NAME	DESCRIPTION
1	Initial	Maintenance and development of the organisations technology infrastructure is performed on an ad hoc basis.
2	Managed	Simple, but complete set of practices defined to support the development and maintenance of the organisations IT infrastructure.
3	Defined	Standard operating procedures are in place to manage IT infrastructure development and maintenance to support patient safety business processes.
4	Quantitatively Managed	A dedicated support team takes ownership of the development and maintenance of the organisations IT infrastructure. Proactive development of infrastructure ensures optimal functioning and up-to-date IT infrastructure.
5	Optimizing	IT infrastructure development and maintenance is focussed on continuous improvement and is performed so as to enable the system to respond to opportunity and change in the future.

INTEROPERABILITY MATURITY LEVEL *Select the level with the most accurate description*	1	SYSTEM AS SILO

LEVEL	NAME	DESCRIPTION
1	System as silo	Development and maintenance is localised to the individual system setting. No standardisation.
2	Peer-to-peer	Guidelines for the development and maintenance of the organisations technical infrastructure are available, but are not followed consistently.
3	Distributed	Development and maintenance of the organisations technical infrastructure is guided by a technology interoperability framework. Streamlining or organisational procedures for knowledge sharing.
4	Integrated	Development and maintenance of technical infrastructure is shared across various heterogenous systems which serve a common goal.
5	Universal	Universal interoperability of the global health information exchange supports adaptation of work processes relating to the development and maintenance of technical infrastructure.

MJ Schurer, L Louw, L Bam, IH de Kock

Results

Maturity Assessment Results

The following results pertain to:

Organisation:

Assessment date:

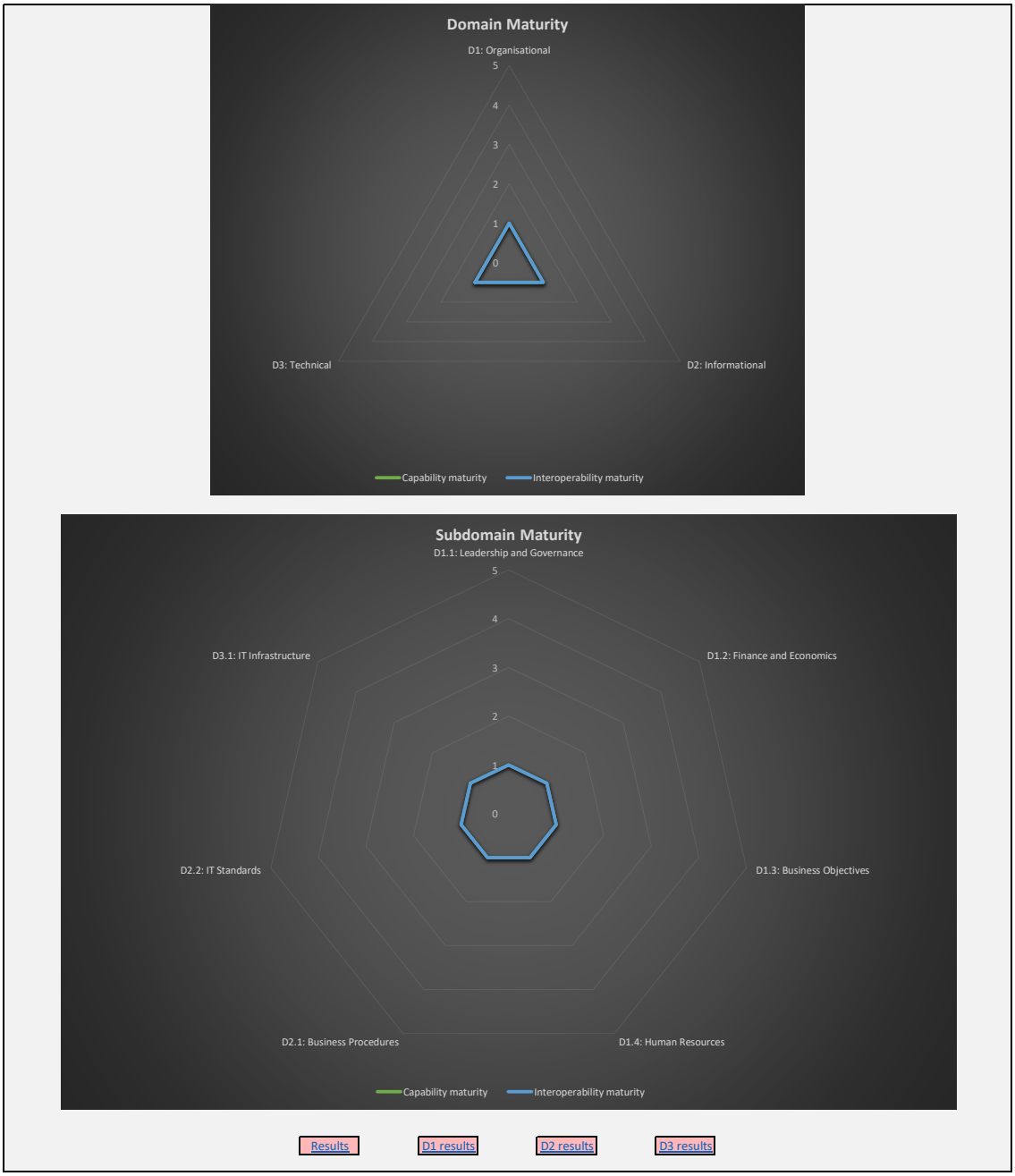
Domain 1: Organisational				
Subdomain 1: Leadership and Governance	**Capability Level**	**Score**	**Interoperability Level**	**Score**
1.1.1 Law, Regulation, and Policy	Initial	1	System as silo	1
1.1.2 Governance structures and commitment	Initial	1	System as silo	1
1.1.3 Business Continuity and Responsiveness	Initial	1	System as silo	1
1.1.4 Data ethics/Ownership	Initial	1	System as silo	1
1.1.5 Monitoring of performance and effectiveness	Initial	1	System as silo	1
1.1.6 Transparency and accountability	Initial	1	System as silo	1
1.1.7 Partnerships	Initial	1	System as silo	1
1.1.8 Stakeholder communication	Initial	1	System as silo	1
1.1.9 Organisational Strategy alignment	Initial	1	System as silo	1
1.1.10 Building a culture of Safety	Initial	1	System as silo	1
1.1.11 Organisational change management	Initial	1	System as silo	1
	Subdomain Score:	**1,00**	**Subdomain Score:**	**1,00**
Subdomain 2: Finance and Economics	**Capability Level**	**Score**	**Interoperability Level**	**Score**
1.2.1 Financial management	Initial	1	System as silo	1
1.2.2 Financial resource mobilisation	Initial	1	System as silo	1
	Subdomain Score:	**1,00**	**Subdomain Score:**	**1,00**
Subdomain 3: Business Objectives	**Capability Level**	**Score**	**Interoperability Level**	**Score**
1.3.1 Regulatory Compliance	Initial	1	System as silo	1
1.3.2 Resource efficiency and business sustainability	Initial	1	System as silo	1
1.3.3 Data management	Initial	1	System as silo	1
	Subdomain Score:	**1,00**	**Subdomain Score:**	**1,00**
Subdomain 4: Human Resources	**Capability Level**	**Score**	**Interoperability Level**	**Score**
1.4.1 Human resources policy	Initial	1	System as silo	1
1.4.2 Human resources capacity	Initial	1	System as silo	1
1.4.3 Human resources capacity development	Initial	1	System as silo	1
	Subdomain Score:	**1,00**	**Subdomain Score:**	**1,00**
	Domain Score:	**1,00**	**Domain Score:**	**1,00**

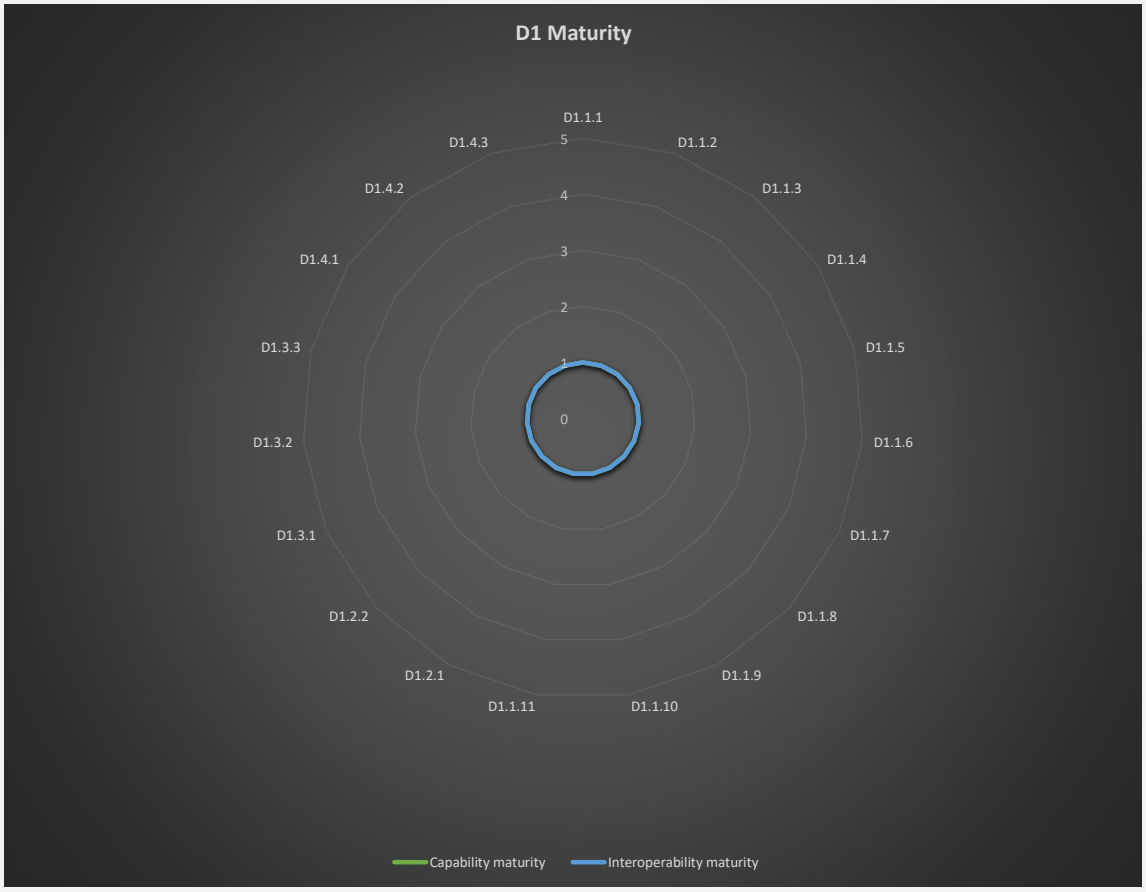
Domain 2: Informational (Syntax and Semantics)				
Subdomain 1: Business Procedures	**Capability Level**	**Score**	**Interoperability Level**	**Score**
2.1.1 Data Capture	Initial	1	System as silo	1
2.1.2 Data Storage and Aggregation	Initial	1	System as silo	1
2.1.3 Workflows	Initial	1	System as silo	1
2.1.4 Data Presentation/Transmission	Initial	1	System as silo	1
	Subdomain Score:	**1,00**	**Subdomain Score:**	**1,00**
Subdomain 2: IT Standards	**Capability Level**	**Score**	**Interoperability Level**	**Score**
2.2.1 Data Standards	Initial	1	System as silo	1
2.2.2 Information content	Initial	1	System as silo	1
2.2.3 Data protection, privacy, and security standards	Initial	1	System as silo	1
2.2.4 Information exchange and interoperability standards	Initial	1	System as silo	1
	Subdomain Score:	**1,00**	**Subdomain Score:**	**1,00**
	Domain Score:	**1,00**	**Domain Score:**	**1,00**

Domain 3: Technical				
Subdomain 1: IT Infrastructure	**Capability Level**	**Score**	**Interoperability Level**	**Score**
3.1.1 ICT Hardware	Initial	1	System as silo	1
3.1.2 Network	Initial	1	System as silo	1
3.1.3 Development and Maintenance	Initial	1	System as silo	1
	Subdomain Score:	**1,00**	**Subdomain Score:**	**1,00**
	Domain Score:	**1,00**	**Domain Score:**	**1,00**

C. CHAPTER 9 SUPPORTING CONTENT

Results as radar charts
Domains and subdomains summary
Domain 1 detailed
Domain 2 detailed
Domain 3 detailed





Domain 1: Organisational

Subdomain 1: Leadership and Governance
1.1.1 Law, Regulation, and Policy
1.1.2 Governance structures and commitment
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1.1.4 Data ethics/Ownership
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1.1.9 Organisational Strategy alignment
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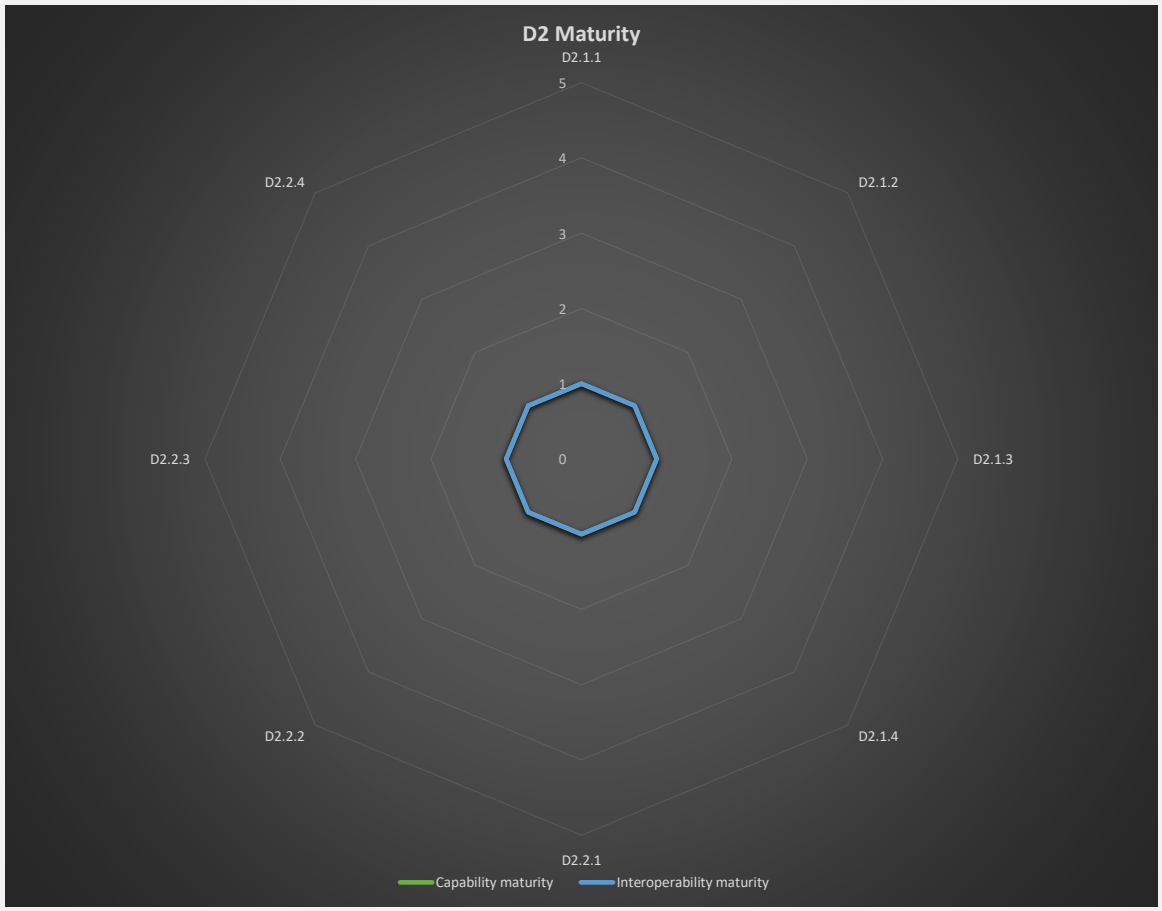
1.1.11 Organisational change management

Subdomain 2: Finance and Economics
1.2.1 Financial management
1.2.2 Financial resource mobilisation

Subdomain 3: Business Objectives
1.3.1 Regulatory Compliance
1.3.2 Resource efficiency and business sustainability
1.3.3 Data management

Subdomain 4: Human Resources
1.4.1 Human resources policy
1.4.2 Human resources capacity
1.4.3 Human resources capacity development

Results D2 results D3 results

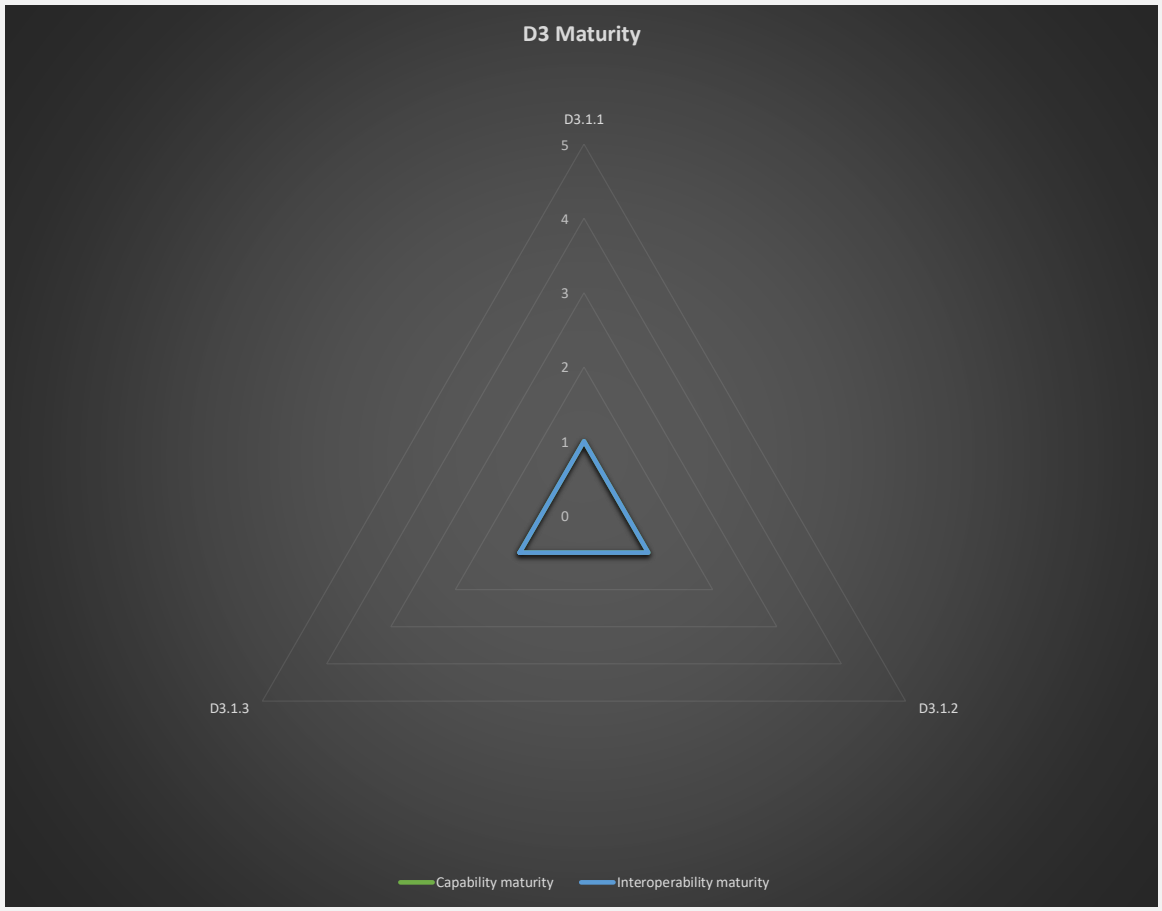


Domain 2: Informational

Subdomain 1: Business Procedures
2.1.1 Data Capture
2.1.2 Data Storage and Aggregation
2.1.3 Workflows
2.1.4 Data Presentation/Transmission

Subdomain 2: IT Standards
2.2.1 Data Standards
2.2.2 Information content
2.2.3 Data protection, privacy, and security standards
2.2.4 Information exchange and interoperability standards

Results D1 results D3 results



Domain 3: Technical

Subdomain 1: IT Infrastructure
3.1.1 ICT Hardware
3.1.2 Network
3.1.3 Development and Maintenance

Results D1 results D2 results

C.3 Letter of request for case study

C. CHAPTER 9 SUPPORTING CONTENT

UNIVERSITEIT iYUNIVESITHI STELLENBOSCH UNIVERSITY 100 1918·2018

30 July 2019

[redacted]

Letter of Request for Case Study

Dear Sir/Ma'am,

My name is Max Schurer, I am completing a PhD in Industrial Engineering at the University of Stellenbosch. My research focus is the interoperability of ICSR collection tools and spontaneous reporting systems in pharmacovigilance. My PhD supervisor is Dr Louis Louw. I am writing to kindly request your help with a case study of your organisation to verify part of my research.

Spontaneous reporting is considered the cornerstone of data generation in pharmacovigilance (PV). The aim of the Pharmacovigilance Reporting Capability Maturity Model (PVR-CMM) is to promote and improve interoperability in PV by addressing the degree of integration of systems involved, provide guidance on which system components need to be improved, as well as provide a means for measuring interoperability progress across the community of spontaneous reporting systems in the global PV landscape.

The case study would involve performing a maturity assessment of your organisation's spontaneous reporting system. It is envisioned that this will require a number of 30-45 minute sessions/interviews with 2-3 relevant members of your organisation at each session, spanning over a period of up to 2 weeks in the month of August 2019. These sessions will not necessarily involve the same people on each occasion. The question of who will need to be present at each session is one which will be best answered by a member of [redacted] who can assist me with identifying the most appropriate [redacted] member/s for each session depending on the topic of the session. The session topics will be based on the seven subdomains of the PVR-CMM, namely: Leadership and governance, Finance and economics, Business objectives, Human resources, Business procedures, IT standards, and IT infrastructure. The intention behind the multiple brief sessions is to avoid causing any disruption to your organisation. The sessions will be held subject to the availability of the contributors.

The materials involved in the case study are the PVR-CMM and a document which will provide some more context regarding the model's development and intended use. Please note that this case study will result in no cost being incurred by [redacted]. The university of Stellenbosch will facilitate and finance all travel and accommodation requirements. Accompanying this letter is a preview of the PVR-CMM in .pdf format. The complete PVR-CMM will be presented during the case study and is an easy to use Excel document.

The findings of this case study will form part of my PhD thesis, however, all information provided during the case study sessions/interviews will be held anonymously and will not allow for traceability back to the original contributor. No personal information will be included in the thesis whatsoever.

In summary, I kindly request the following:

- Confirmation of your willingness to participate in this case study,
- Assistance with identifying the appropriate contact person from [redacted] who I can meet with in [redacted], to plan the sessions (identify relevant [redacted] contributors) and the timelines associated with the information sessions.

- A proposed date for the above-mentioned meeting (In person would be preferable), or a proposed starting date.

In return for your cooperation with this case study your organisation will receive a formal maturity assessment via the PVR-CMM, as well as several recommendations for continuous improvement initiatives once the feedback has been appropriately analysed. If you require any additional information, or have any questions please don't hesitate to contact me (details below).

Thank you very much for your time and I look forward to working with your organisation,

Kind regards,

Maximillian J. Schurer
PhD Industrial Engineering candidate (Full time)

saam vorentoe · masiye phambili · forward together

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